

THE ASSOCIATION BETWEEN PHYSICAL ACTIVITY AND COGNITION: THE BALTIMORE EXPERIENCE CORPS TRIAL

**By
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Abstract

Background

Because of population aging, the number of people with AD is expected to triple (11-16 million) by 2050. Over the past decade pharmaceutical interventions focused on AD have had minimal success in targeting the underlying pathology of the disease and modifying disease course. Because of these difficulties, research focus has recently expanded from disease modifying pharmaceutical therapies to lifestyle interventions. Physical activity in particular may have beneficial effects on cognition and brain health, however older adults – especially those with socio-demographic risk factors – are becoming increasingly inactive and have difficulty initiating and adhering to exercise programs. Understanding and evaluating the nature of the benefits of low-intensity activity, the characteristics of dose required to achieve health benefits, and the mechanisms of change particularly within low socio-economic status (SES) populations is essential to designing sustainable lifestyle interventions that can be easily and effectively integrated into communities. The aims of this dissertation are to 1) better characterize and understand the relationship between objectively measured low-intensity physical activity and cognition; 2) inform the feasibility of a civic-engagement volunteer service program to increase physical activity in a socio-demographically at risk population; and 3) explore the potential of objective physical activity devices to be used as biometric signals of disability.

Methods

The study sample is from the Baltimore Experience Corps Trial (BECT), an intention-to-treat, randomized, controlled effectiveness trial, and the Brian Health Study (BHS), a substudy within the BECT. Physical activity was measured using both objective and self-report measures. Cognitive measures included domain specific psychometric measures and neuroimaging measures obtained from structural brain imaging. Physical function measures included both performance-based and self-report measures.

Results & Conclusions

Objective measures of physical activity within the low-intensity range were associated in cross-section with physical function and both behavioral and structural measures of brain structure.

These objective measures, which are important in order to characterize physical activity and change particularly within the low-intensity range, captured increases in total and low-intensity walking activity associated with the intervention in women within the BECT, and a decrease in moderate- to vigorous-intensity walking activity in men. Self-report measures of physical activity did not sensitively capture low-intensity physical activity or the relationship between physical activity and cognition; however, as expected, sensitively captured moderate- to vigorous physical activity and its association with physical function. Self-report measures additionally indicated declines across both intervention arms in women within the BECT and marginal negative intervention effects particularly in moderate- to vigorous-intensity physical activity, and captured declines in the control group for men, and positive intervention effects at 24 months. Objective measures are extremely useful in order to sensitively capture physical activity, and can be used in order to better measure and understand the relationship between physical function/ activity and cognition.

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Chapter 1.

Introduction and specific aims

Overview

Public Health Significance

The estimated 2012 prevalence of Alzheimer's Disease (AD) in the United States is 5.4 million ¹. Because of population aging, the number of people with AD is expected to triple (11-16 million) by 2050 ¹. Over the past decade pharmaceutical interventions focused on AD have had minimal success in targeting the underlying pathology of the disease and modifying disease course ²⁻⁵. Because of these difficulties, research focus has recently expanded from disease modifying pharmaceutical therapies to lifestyle interventions that may show more promise in preventing AD and cognitive decline.

The potential of physical activity

In their 2010 State of the Science Conference, the NIH recognized promising research underway on physical activity that may provide insight into ways to prevent or delay cognitive decline and AD ⁶. Evidence indicates that increasing physical activity may have indirect, beneficial effects on cognition through the reduction in risk of diseases related to diminished cognition (e.g., cardiovascular disease, type II diabetes) ⁷, as well as direct effects through a variety of mechanisms (e.g., up-regulation of neurotrophins related to neurogenesis) ^{8,9}.

Difficulties related to increasing physical activity

Although physical activity may be cognitively beneficial, older adults are becoming increasingly inactive ¹⁰ and have difficulty initiating and adhering to exercise programs ¹¹⁻¹³. Additionally, for many older adults with socio-demographic risk factors, a lack of physical activity opportunities due to restrictive environmental and neighborhood characteristics creates additional barriers to increasing physical activity ¹⁴.

Research recommendations

Given the large proportion of older adults who are chronically inactive or unfit, the most recent physical activity guidelines published by the United States Department of Health and Human Services recommended additional observational and experimental studies to evaluate the nature of the benefits of low-intensity activity, the characteristics of the dose required to achieve health benefits, and the mechanisms of change particularly within low socio-economic status (SES)

populations ¹⁵. The 2010 NIH Consensus Panel additionally recommended studies examining dose-response relationships between objectively measured physical activity and cognition/ brain health ⁹.

Towards a solution

The results of this thesis offer the potential to: 1) better characterize and understand the relationship between objectively measured low-intensity physical activity and cognition; 2) inform the feasibility of a civic-engagement volunteer service program to increase physical activity in a socio-demographically at risk population; and 3) explore the potential of objective physical activity devices to be used as biometric signals of disability.

Specific Aims

Aim 1A: Explore adherence to U.S. Department of Health and Human Services physical activity guidelines and the cross-sectional association between objective and self-report measures of physical activity and physical function.

Hypotheses 1A: The SAM will be able to capture a range of low-intensity walking activity; SAM metrics of low-intensity activity will be associated in cross-section with significant physical function outcomes related to independent function including mobility difficulty and lower extremity function.

Aim 1B: Explore the cross-sectional association between objective and self-report measures of low-intensity physical and walking activity and cognitive function/ brain health.

Hypothesis 1B: Low-intensity walking activity measured by the SAM will be associated with executive function, as well as memory and hippocampal volume. CHAMPS measure will not be associated with cognitive function/ brain health due to a lack of sensitivity of measurement.

Aim 2A: Explore whether the EC intervention was associated with increased walking activity measured by an objective physical activity measurement device.

Hypothesis 2A: Participants randomized to the intervention arm of the Baltimore Experience Corps Trial (BECT) will show increased walking activity - specifically within the low-intensity range – after two years.

Aim 2B: Explore whether the EC intervention was associated with increased physical activity measured by a self-report questionnaire.

Hypothesis 2B: Due to the lack of sensitivity of subjective measures of physical activity, the CHAMPS will not show intervention-related change in physical activity across intensities.

AIM 3: Explore the relationship between physical activity and physical function in order to inform the use of objective physical activity devices as biometric signals to predict cognitive decline and disability.

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Chapter 2.

Background

Public health significance of cognitive decline

Ranging from age-related cognitive decline and mild neurocognitive impairment to major neurocognitive impairment, cognitive decline is a major cause of disability and morbidity among older adults in the U.S.³. Alzheimer's Disease (AD), the most common subtype of major neurocognitive impairment and one of the main causes of significant cognitive decline, is the sixth leading cause of death in the U.S.; costs for care are estimated to be \$200 billion in 2012⁴. Based on recent projections by the U.S. Census, by 2050 approximately one third of the U.S. population will be over 65, resulting in a doubling of the annual incidence of AD and other dementias⁴. In addition to the aging of the U.S. population, declining fertility rates are expected to result in the insolvency of entitlement programs including Social Security, Medicare, and Medicaid⁵. Because these programs cover the majority of healthcare costs for people with AD^{4,6}, particularly those of low socio-economic status (SES), there is a research imperative to develop preventive interventions that can increase the number disability free life years for older adults. Shifting the onset of major neurocognitive impairment by six months to one year can save billions in health

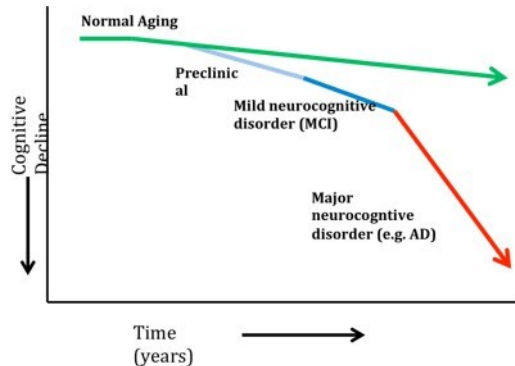


Figure 1: Progression from normal aging to major neurocognitive disorder; Adapted from Institute for Memory Impairments and Neurological Disorders, University of California Irvine [http://www.alz.uci.edu/alzheimers-disease/mci-the-transition-from-normal-aging-to-dementia/]

care dollars⁷ and significantly reduce burden at the individual, family and societal level.

The relationship between age-related cognitive decline, mild neurocognitive disorders (MCI*) and major neurocognitive disorders such as AD can be conceptualized as a progression (Figure 1). While there are therapies to improve the quality of life for patients with major neurocognitive disorders, currently there are no interventions that can permanently reverse pathology and symptoms⁸.

Therefore, preventive interventions that target individuals early, during the normal, preclinical and MCI stages of cognitive decline – prior to the development of impairment such as AD – are essential.

* The DSM-5 renamed mild cognitive impairment (MCI), mild neurocognitive disorder. We use the acronym MCI to refer to the updated nomenclature.

Cognitive decline

Cognitive decline characterizes age-related cognitive decline and neurocognitive disorders ranging from mild to major chronic disorders of various etiological subtypes (e.g., AD, vascular dementia, fronto-temporal dementia, etc.).[†] Cognitive decline refers to a deterioration in the ability to perform within any of the specific cognitive domains (memory, attention, executive function, visuospatial skills, language, social cognition;⁹) or global/ general cognition. Below we elaborate on the domains of cognition and associated brain structures, impairments characterized by cognitive decline, and briefly, the tools used to measure global and domain specific cognitive decline and cognitive impairments.

Cognitive domains

Depending on the field and purpose of inquiry, the number and definition of cognitive domains vary. We consider the neurocognitive domains identified by the neurocognitive disorders working group of the American Psychiatric Association DSM-5 Task force^{9, 10}. Memory, the process by which information is encoded, stored and retrieved, is the most studied domain in cognitive aging. It includes long-term memory – split further into declarative (implicit) and non-declarative (explicit) components – and working memory, a concept that replaced the unitary concept of short-term memory¹¹. Many underlying brain structures are associated with memory. The dorsolateral prefrontal cortex (PFC), located in the anterior part of the frontal lobes of the brain, is associated with working memory; the left PFC is involved in more verbal tasks, and the right is involved in visuospatial tasks^{12, 13}. The medial temporal lobes and the hippocampus, in addition to the PFC, are involved in episodic memory, a sub-component of declarative memory¹⁴. Other brain regions, including the basal ganglia, cerebellum, posterior neocortex, and temporal cortical regions are associated with other types of memory including implicit, procedural, and semantic memory¹². Attention is the process of concentrating on one stimulus while ignoring others. Attention includes components of processing speed and executive control/ function, and is associated with the PFC¹⁵. Executive function, which overlaps partially with attention and

[†] The diagnosis of mild to major characterizes all neurocognitive disorders in the DSM-5 other than delirium, a disturbance of consciousness that develops quickly, tends to fluctuate, and is typically associated with temporary disease conditions such as urinary tract infections in the elderly.

memory, includes cognitive processes related to strategic organization and complex goal-oriented tasks. The PFC, specifically the frontal-striatal circuits, as well as connections with posterior cortical regions, are associated with executive functions ¹⁶. Visuospatial skills include cognitive processes related to analyzing and manipulating objects in space. The brain regions associated with these processes are not fully understood, however may be mostly in the right cerebral hemisphere, and include inferior parietal and posterior parietal regions ¹⁷. Language, or linguistic knowledge, includes cognitive processes related to communication and discourse. The associated brain regions include Broca's frontal area located in the posterior region of frontal lobe near the temporal cortex of the left hemisphere, and Wernicke's area located in the posterior section of the superior temporal gyrus ¹⁸. The mental lexicon (i.e., semantic knowledge) and mental grammar (i.e., syntactic knowledge) are considered components of language ¹⁹. The mental lexicon refers to stored information including all idiosyncratic, word-specific information. Mental grammar refers to the syntactic rules that govern language. These components have been conceptualized using the declarative and procedural memory model, where declarative memory system underlies the mental lexicon and procedural memory underlies mental grammar ¹⁹. Social cognition includes knowledge about the self, perceptions of others and other cognitive processes related to social function. While this domain may be associated with a network of brain regions, recent evidence shows that the medial frontal cortex, including the anterior cingulate cortex (ACC), is strongly associated with social cognition ²⁰. While this domain is not traditionally viewed as a domain of cognition by cognitive psychologists and neuroscientists, it is identified in the DSM-5 as one of the cognitive domains important for diagnosis of neurocognitive impairment ⁹.

Age-related cognitive decline

Also considered normal cognitive aging, age-related cognitive decline refers to decline associated with increasing age in the absence of disease. Many cognitive domains exhibit age related decline in the last four decades of life ²¹ †, however, some studies have found that this decline is slow and minimal in older adults with less neuropathology ²².

The two overarching hypotheses explaining age-related cognitive decline include the processing-speed hypothesis and process-specific hypothesis ²³. The processing-speed hypothesis posits that

† Some aspects of cognition, including crystallized intelligence, world knowledge, and verbal ability may stay constant or even improve with age.

age-related cognitive declines are driven by declines in processing rates ²⁴. This hypothesis assumes that performance on cognitive tasks across domains is limited by general cognitive processing capacity and speed of processing is the critical constraint associated with increasing age ²⁴. Although the hypothesis does not exclude the importance of domain-specific age-related effects, it states that the variability in age-related differences in cognition can be at least partially accounted for by processing speed differences ²⁵. The two mechanisms explaining how processing speed affects cognition and performance on cognitive tasks are the limited time mechanism and simultaneity mechanism. The limited time mechanism states that time to perform future tasks is restricted when available time is occupied by continuing to perform, or execute, past tasks. The simultaneity mechanism states that the results of earlier tasks may be lost before they are needed for future tasks ²⁴. Both mechanisms clearly implicate executive function as essential to our understanding of age-related cognitive decline.

The process-specific hypothesis, which often focuses on executive control, suggests that declines are due to deficits in inhibitory control, task switching, and coordination ability ²³. In 1988, Hasher et al. proposed that inhibition, or the ability to control access to attention's focus, deletes irrelevant information from attention and working memory, and suppresses responses, was central to the operation of working memory and attention ²⁶. Aging related declines in working memory, for example, may be understood as declines in the ability to inhibit; as inhibitory processes break down, non-goal related tasks or processes enter into working memory resulting in unprocessed goal-related tasks or processes. Evidence for inhibition as the major source of cognitive performance differences due to age, or the inhibitory deficit theory, is summarized in a chapter by Lustig et al. ²⁷.

Considering the specific cognitive domains, components of memory, including working memory and long-term memory decline with age however at different rates ²⁸. Many studies show that the pre-frontal cortex and the medial temporal lobe, including the hippocampus, (the approximate location of working memory and non-declarative memory) are most sensitive to age-related changes, while the neo-cortex (the approximate location of semantic and procedural memory) is less affected by age ²⁸⁻³⁰. Attention, executive function, and visuospatial skills additionally decline with age. Attention, including selective, divided, switching, and sustained attention, measured using various psychometric tests (e.g., Stroop test) as well as structural and functional imaging of the frontal lobes, shows clear declines with age ¹⁵. Age-related decline in

executive function are structurally and functionally linked to volumetric degeneration in the PFC³¹⁻³³. Age-related declines in visuospatial skills are related to dedifferentiation of the ventral and dorsal processing streams that process the visual features of objects and information on their spatial location^{34,35}. Unlike many other cognitive domains, language abilities generally improve over the life course³⁶. In general, semantic processing is maintained with age, while complex syntactic processing, which requires components of working memory, declines³⁶. Normal aging seems to be associated with declines in social cognition due to declines in functional connectivity³⁷ and may be associated with declines in knowledge structures and processing mechanisms³⁸.

In general, cognitive decline reflected in behavior (performance on cognitive tests) begins during the 20s and 30s in healthy, educated adults according to many cross-sectional studies³⁹, or during the 50s and 60s according to longitudinal studies⁴⁰. It is important to note that not all individuals experience cognitive decline as they age, and certain domains and sub-domains may decline while others remain preserved¹². Therefore, the question of whether age-related decline is an abnormal state, and whether it can be considered impairment is often debated. What is clear is that the heterogeneity across individuals in terms of age-related decline provides insight into various biological and behavioral factors that may help to preserve cognition into older ages.

Mild neurocognitive disorders (MCI)

Considered the “pre-dementia” phase, MCI is a clinical stage prior to the onset of major neurocognitive disorder^{41,42}. The diagnostic criteria for the disorder according to DSM-5 criteria include evidence of modest cognitive decline in one or more cognitive domains from a previous level of performance, and no evidence of loss of independence in activities of daily living⁹. The disorder is further separated into subtypes where AD is the most prevalent. The MCI criteria specific to neurodegenerative diseases (e.g., AD, Vascular Dementia, Lewy Body Disease, Frontotemporal Dementia) formalized by Petersen et al⁴² and further developed by Winblad et al⁴³ and Lopez et al⁴⁴ separated MCI into two categories: amnesic MCI (aMCI), or MCI characterized by declines in memory and/or other domains, and non-amnesic MCI (naMCI), or MCI characterized by declines in one or more domains not including memory. The diagnostic criteria for aMCI and naMCI are included within the appropriate subtypes in the DSM-5.

Major neurocognitive disorders

According to the DSM-5, the etiological subtypes of major neurocognitive disorders include AD, Frontotemporal lobar degeneration (FTD), Lewy body disease, Vascular disease, Traumatic brain injury, Substance/medication-induced, HIV infection, Prion disease, Parkinson's disease, Huntington's disease, and major neurocognitive disorders due to another medical condition, multiple etiologies, or unspecified. The neurodegenerative subtypes (considered dementias), generally include AD, FTD, Lewy body disease, and Vascular disease. Based on the two most often cited studies estimating dementia prevalence (Chicago Health and Aging Project (CHAP) & Aging, Demographics, and Memory Study (ADAMS)), 60-80% of dementia cases are attributable to AD ⁴⁵.

AD has an insidious onset and gradual progression of impairment. The three main diagnostic criteria include: 1) evidence of a decline in memory and learning as well as a decline in at least one other cognitive domain; 2) Steadily progressive, gradual decline in cognition without extended plateaus; 3) No evidence of mixed etiology.⁵ Additionally, clinicians consider evidence of a genetic mutation associated with AD ⁹. There are a number of diagnostic markers for AD including cortical atrophy, amyloid neuritic plaques, and tau neurofibrillary tangles ⁹. Many of those markers can only be confirmed by post-mortem histopathological examination. The genetic

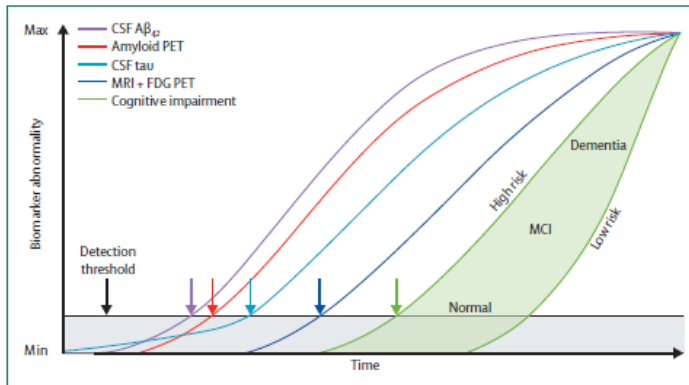


Figure 2: Model integrating Alzheimer's disease immunohistology and biomarkers (from ²)

manifestation of biological changes in the brain. While the majority of research on cognitive aging has been based on behavioral measures (e.g., speed and accuracy), recently brain-based biomarkers have been used to measure cognitive decline and test previous theories concerning trajectories of decline ⁴⁶.

mutation E4 Apolipoprotein E (APOE) is considered a significant risk factor for AD.

Tools to measure cognitive decline and impairment

Non-genetic, non-developmental cognitive impairment characterized by cognitive decline is the clinical

⁵ The Neurocognitive Disorders Work Group of the American Psychiatric Association's (APA) DSM-5 Task Force, removed functional impairment from the diagnostic criteria, emphasizing that it was a consequence of the disease, not a criteria for diagnosing the disorder (see ref: 22).

Jack et al.'s 2013 paper on tracking the pathophysiological processes in AD, an updated version of his 2010 paper, provides a compelling argument for the importance of various measures of cognitive decline and impairment considering the temporal process of AD ^{2, 47}. The authors describe the behavioral and clinical manifestations of AD as preceded by detectable abnormality increases in cerebrospinal fluid (CSF) AB concentration, amyloid deposition imaged through PET, CSF tau concentration, and brain atrophy in specific regions including the hippocampus (Figure 2) ². Because the behavioral and clinical manifestations may signal an irreversible process toward impairment, the use of a range of temporal specific biomarkers to identify those at risk is critical for identifying windows of intervention where researchers and clinicians can intervene in order to delay or reverse decline.

Therapeutic interventions to delay AD and cognitive decline

Prevention of dementia has been a key focus of a number of pharmaceutical trials. Although those trials have had minimal success in preventing dementia, they have been able to alleviate some of the symptoms of disease and have provided insight into the evolving pathology of the disease ⁴⁸. In 2010, the NIH put together a panel evaluating factors associated with reduced risk of AD and cognitive decline; they outlined their assessments of therapeutic interventions with randomized controlled trial (RCT) designs that were at least 2 years in duration and adequately powered ³.

Concerning AD, the statement reported that: 1. No current vitamin, nutrient, and dietary supplements have been found to affect the onset of AD (this included the recent Vitamin E and ginkgo biloba trials); and 2. There is no known medication that can delay the onset of AD (this includes RCTs evaluating the performance of cholinesterase inhibitors, anti-hypertensive medications, and hormone replacement). Concerning cognitive decline, the statement reported that in general, few existing studies showed a clear association between many risk and protective factors, and cognitive decline. This included nutritional and dietary factors (longer chain omega-3 fatty acids show the most promise), medications (including statins, anti-hypertensives, and anti-inflammatory drugs), socioeconomic factors (Note: While the Rotterdam study ⁴⁹ was the first to show an inverse, dose-response association between education and dementia, other studies have shown that education may only mask the behavioral and functional symptoms of cognitive decline resulting in a steeper trajectory of decline once symptoms begin to present ⁵⁰), social and

cognitive engagement, past smoking and alcohol use, genetic factors (Note: The panel's statement suggests that while ApoE gene variation has been associated with greater cognitive decline in the elderly, it does not seem to affect all cognitive domains). The studies that have shown a clearer association with cognitive decline include medical factors (specifically cardiovascular risk factors including high blood pressure and metabolic syndrome), psychological and emotional health (including depression and depressive symptoms), and current smoking. They concluded that was no firm evidence about "the association of any modifiable risk factor with cognitive decline or Alzheimer's Disease" and "evidence is insufficient to support the use of pharmaceutical agents or dietary supplements to prevent cognitive decline or Alzheimer's Disease" ³.

Although the panel admitted that the evidence for most interventions is insufficient to support recommendations, they did additionally conclude that there was preliminary evidence showing that physical activity interventions may inform both the pathological process of AD and cognitive decline as well as prevention efforts. Currently, these interventions hold great promise to affect the course of AD and cognitive decline.

Physical activity

Recent advances in measurement techniques, in addition to epidemiological findings from observational studies, have begun to provide human research support to a large body of non-human research showing the cognitive benefits of physical activity ⁵¹. Below we elaborate on the definition and measures of physical activity, the epidemiological evidence, and more recent neurophysiology and imaging research supporting the association between physical activity and cognition, an overview of the potential mechanisms explaining the association, and current gaps and areas to address.

Definition and measures of physical activity ⁵²

Physical activity can be considered any activity that increases energy expenditure above a resting level ^{53, 54}. Activity can include non-exercise leisure-time/ life-style activities (e.g., walking, gardening, etc.), instrumental activities of daily living (e.g., shopping, housework, etc.), and exercise (lifting weights and running) ⁵⁵, and can vary in intensity from low (<3.0 metabolic

equivalents (METs)) to moderate to vigorous (≥ 3.0 METs)⁵⁶. Low-intensity activities include those related to standing and casual walking and moderate to vigorous intensity activities can include those related to exercise that causes moderate to large increases in breathing/ heart rate^{55, 56}. Studies exploring the relationship between physical activity and cognitive health, most often use self report questionnaires, including the Community Health Activities Model Program (CHAMPS)⁵⁷ and the Minnesota Leisure Time Activity Questionnaire (MLTA)⁵⁸, which convert frequency and amount of time spent on various activities to energy expenditure, or METs. Objective measures of daily activity using pedometers and accelerometers are less commonly used in large studies due to increased cost of implementation and participant compliance⁵⁹. Even less often used are measures of aerobic capacity, or fitness, including Forced Expiratory Volume (volume of air that can be blown out in 1 second, FEV); and VO₂ max (peak oxygen uptake) obtained during exercise on a treadmill.

Epidemiological evidence of cognitive benefits

The relationship between physical activity and dementia has been shown in a number of large-scale observational studies: Nurses Health Study⁶⁰; Cardiovascular Health Cognition Study⁶¹; Adult Changes in Thought Study⁶²; Canadian Study of Health and Aging⁶³. There have been a few important exceptions where physical activity was not associated with a lower risk of dementia^{50, 64-66}. The majority of epidemiological studies have relied on self-report questionnaires, which have been shown to underestimate physical activity⁶⁷, not account for variable definitions of exercise, and not effectively record the contribution of functional activity to exercise⁶⁸. Recently, a study using objectively measured physical activity (accelerometers) showed that greater total daily physical activity was associated with reduced risk of AD⁶⁹.

The MacArthur Studies of Successful Aging were among the first, large-scale, longitudinal epidemiological studies to show a relationship between late-life physical activity and cognitive health among non-demented older adults: FEV and strenuous activity (energy expended during strenuous activities of daily living around the house) predicted global cognitive decline over 2.5 years on a composite cognition score that included five domains of cognition: language, non-verbal memory, verbal memory, conceptualization, and visuo-spatial memory⁷⁰. These findings have been replicated in other large-scale, longitudinal epidemiological studies in non-demented older adult populations using various measures of physical activity, ranging from intensity and

frequency of exercise and sports activity to variety of leisure time activities and global or composite measures of cognition. In addition, women with higher levels of baseline physical activity were less likely to develop cognitive decline on the MMSE ⁷¹ and performed better on a composite cognition score ⁶⁰. In 2008, the Cochrane Review published a review including 11 randomized clinical trials of aerobic physical activity programs and concluded that, although there was evidence for the benefit of aerobic physical activity on cognitive function – specifically motor function, cognitive speed, delayed memory functions, and auditory and visual attention – further studies needed to determine whether the effect was due to improvements in cardiovascular fitness ⁷². Also, in their review of physical activity and the maintenance of cognitive function, Rockwood et al. concluded that there was a dose-response relationship between physical activity and the preservation of cognitive function, and posited that small increases in activity from a sedentary state can yield a large incremental benefit ⁷³.

Neurophysiology and imaging evidence of brain health benefits

With recent advancements in measurement of cognition through neuroimaging and neurophysiology methods, researchers have begun to better understand the potential mediators of the physical activity- cognition relationship. As described in Hilman et al's perspective article in *Nature Reviews*, over the last two decades, electroencephalogram (EEG) data have provided evidence that aerobic fitness and physical activity is associated with greater modulation of the P3 component (related to the amount of attention required to encode a stimulus and the speed of response) generated by the ACC, infero-temporal lobe, and parietal cortex. Additionally, smaller error-related negativity (ERN) amplitude following an error is associated with more active older adults ⁵¹.

Magnetic resonance imaging (MRI) and functional magnetic neuroimaging (fMRI) studies in humans have additionally provided valuable insight into potential mediators. Colcombe et al. found significant increases in brain volume, measured using MRI in participants randomized to an aerobic intervention program ⁷⁴, and found that short-term (six months) cardiovascular fitness training resulted in greater activation in the middle frontal gyrus and the superior frontal gyrus and less activity in the ACC measured using fMRI ⁷⁵. Pereira et al. were the first group to show that in humans, aerobic exercise was associated with regional specific increases in cerebral blood

volume (CBV) in the dentate gyrus of the hippocampus ⁷⁶. Over the last four years, Erickson et al. have extended this work, implicating the hippocampus as a key mediator between physical activity and cognition. In cross-sectional and longitudinal studies related to a physical exercise trial (aerobic walking exercise group compared to a stretching and toning group) Erickson et al. have shown that cardiovascular fitness (measured by VO2 max) was associated with left and right hippocampal volume after controlling for age sex and years of education ⁷⁷. They additionally showed that exercise training selectively increases hippocampal volume by 2% (roughly equivalent to 1-2 years of age-related volume loss)⁷⁸, and the increase was mediated by greater serum levels of blood-derived neurotrophic factor (BDNF), one of a group of neurotrophins – protein growth factors that induce the survival, development, and function of neurons.

Mechanisms of benefit

A number of different mechanisms have been proposed to explain the relationship between physical activity and cognition. Increased cerebral blood flow, the neurogenesis in the hippocampus and the up-regulation of BDNF are among the prevailing hypotheses. Our understanding of cerebral blood flow as a mediator between physical activity and cognition comes mostly from animal models. Endres et al. demonstrated that regular running in rats up-regulates endothelial-derived nitric oxide synthase (eNOS) expression, which has beneficial vascular effects (NO is a vasodilator that increases cerebral blood flow levels). This led to a reduction in cerebral infarct size, brain swelling, and reduced neurological deficits ⁷⁹. Swain et al. demonstrated that prolonged elevated motor activity increases cerebral perfusion in the motor cortex, which may be in turn associated with a number of potentially beneficial outcomes including an increase in the number of capillaries, relaxation of arterioles, increase in size/number of extracerebral vessels, or an increase in tissue oxygen utilization ⁸⁰. As mentioned previously, Pereira et al. demonstrated that exercise increases cerebral blood flow in rats regionally specific to the dentate gyrus (the area of the hippocampus particularly vulnerable to aging effects). This increase also correlated with cardiopulmonary and cognitive function ⁷⁶. In human studies, reduced cerebral blood flow has been shown to be associated with both hypertension and other CV risk factors that can lead to AD pathology. The critically attained threshold of cerebral hypoperfusion (CATHC) cascade, coined by De La Torre, provides a mechanisms to explain the association with AD: 1) Cerebral blood flow declines with age and other risk factors including reduced physical activity; 2) Lower cerebral blood flow lowers the delivery of glucose and oxygen to neurons and glia; 3) A

reduction in brain metabolic energy causes a series of metabolic events that result in destabilized neurons, synapses, neurotransmission, and intellectual function, which results in the formation of AD pathology (senile plaques, amyloid angiopathy etc.)⁸¹.

The majority of human research support for the hippocampus and BDNF as the main mediators between aerobic fitness and cognition come from work mentioned previously by Erickson et al. Their 2009 and 2011 papers made a case for neurogenesis in the hippocampus driven the up-regulation of BDNF^{77, 78}. These findings support a host of animal-research evidence. Physical activity, usually in the form of voluntary wheel running, has been shown to be consistently associated with adult hippocampal neurogenesis^{82, 83}. Studies have additionally found that voluntary running specifically alters the dendritic morphology of dentate gyrus neurons by increasing their length, complexity, and density. This in turn was is associated with improvements on learning and memory tasks⁸⁴. The mechanism driving the relationship has additionally been explored in multiple animal studies. BDNF has been consistently shown to be up-regulated during physical activity^{85, 86}.** BDNF promotes neurogenesis (including differentiation, extension, and survival) in hippocampal, cortical, striatal, septal, and cerebellar neurons, and has been shown to protect the hippocampus and cortex from ischemic damage^{87, 88}. Cotman and Berchtold identified numerous pathways involving exercise and BDNF. They provided evidence for the role of neurotransmitters Acetylcholine (ACh) and gamma-aminobutyric acid (GABA), which are released during exercise, in controlling BDNF gene expression; the association between lower estrogen and decreased hippocampal availability of BDNF (the presence of estrogen may therefore be necessary for exercise-induced neurogenesis); the harmful effect of stress (corticosteroids) on neuronal health and the beneficial effect of exercise on reducing stress; and the role of IGF-1 growth factor⁸⁹, which is released during exercise, on inducing BDNF gene expression⁹⁰. Increased BDNF has been shown in animal and human models to directly induce neurogenesis, dendritic expansion, and memory formation^{91, 92}.

Although many human research studies have explored the relationship between physical activity and cognition using aerobic/ cardiovascular fitness measures as a marker of physical activity,

** IGF-1, another neurotrophic factor, has also been shown to be critical in neurogenesis: mice with low IGF-1 serum levels (associated with older age) showed minimal angiogenesis (associated with the need for new nutrients due to the proliferation of neurons) after physical activity (see ref: 100)

cardiovascular fitness may not fully explain the physical activity – cognition relationship. In three meta-analyses covering different cross-sectional and longitudinal studies, results show that there was no significant linear or curvilinear effect of cardiovascular fitness on cognition despite clear evidence of a relationship between physical activity and cognition⁹³⁻⁹⁵. Etnier et al. proposed that cardiovascular/ aerobic fitness may be the first of a cascade of events that leads to an increase in cognitive performance, and therefore aerobic fitness as a standalone variable may not be sensitive enough to capture cognitive change⁹³.

Kemperman et al. provide an additional explanation for brain plasticity outside the cardiovascular fitness hypothesis. They couple exercise with environmental enrichment – considered cognitive stimulation through social interactions and novelty – in explaining the hippocampal neurogenesis pathway. Environmental enrichment was an important paradigm among early developmental psychologists studying the effect of environment, compared to genetics, on a multitude of factors and outcomes. Animal studies have shown the influence of the environment on brain structure and function⁹⁶, providing some evidence for the importance of complexity and novelty as a key stimuli for neuronal development. Although animals in their natural environment certainly exhibit a large degree of physical activity, physical activity alone does not seem to explain the effects of the environment⁹⁷. Kempermann et al. explain that, “In animals, most if not all aspects of cognition are inseparable from locomotion and physical activity. Exploration, spatial navigation, and most types of learning accessible in a rodent are based on its movement in the outer world. Search for food, shelter, and mates are physical activities requiring mental input to be successful on both a phylogenetic and ontogenetic scale”⁹⁸. They continue to argue that locomotion stimulates and proliferates precursor cells of adult neurons, and environmental enrichment promotes the survival of the neurons to adulthood. Although measuring environmental enrichment (which includes social interactions, novelty, etc.) is difficult, this coupling mechanism provides an elegant explanation for the relationship between physical activity and cognition that extends the cognitive benefits of physical activity beyond aerobic fitness⁹⁸.

While evidence supports physical activity as a potential intervention to maintain and improve cognitive and brain health, the majority of human-research provides evidence for the pro-cognitive effects of aerobic fitness and exercise-related physical activity. For many older adults,

particularly those of low SES, initiating and adhering to exercise programs is difficult ⁹⁹⁻¹⁰². Older adults of lower SES have lower baseline levels of physical activity than higher SES older adults ^{103, 104}, and have access to fewer physical activity-related facilities due to restrictive environmental and neighborhood characteristics ¹⁰⁵⁻¹⁰⁷. This, in combination with the association between low SES and cognitive decline, places lower SES individuals at a “double disadvantage,” where individuals are both at risk for a negative health outcome and are less likely to engage in behaviors that may reduce risk for that outcome.

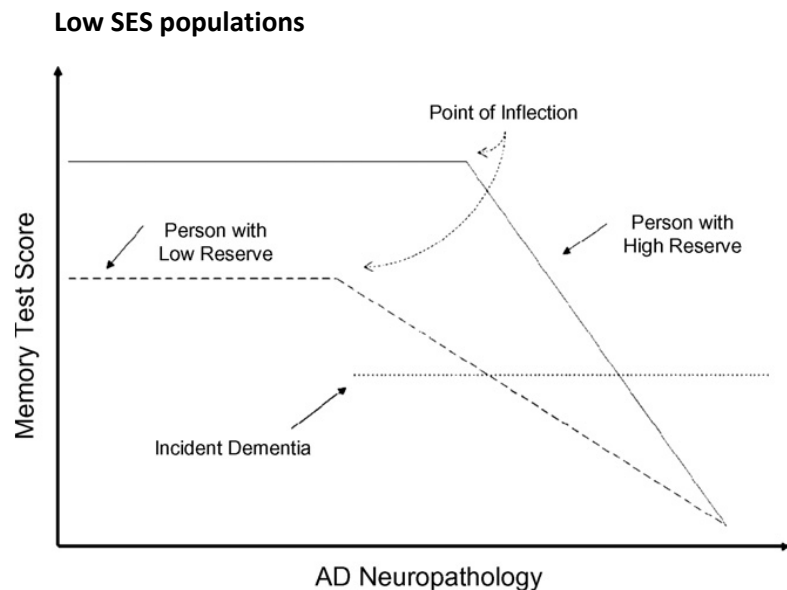


Figure 3: Illustration of cognitive reserve; (from ¹)

In general, lower SES, typically measured by education, income, and occupational attainment, is a risk factor for cognitive decline, including age-related cognitive decline and major neurocognitive disorders such as AD ¹⁰⁸. The term cognitive reserve has been often used to explain the influence of SES (education in particular) on

cognition ¹⁰⁹. The theory considers a reserve model where the brain actively copes and/or compensates for disease pathology resulting in clinical or behavioral manifestations that are “better” than what would be expected considering the extent of brain pathology or damage ¹⁰⁹. Epidemiological evidence suggests that the risk of incident dementia is higher in less educated individuals, and for individuals with the same pathology and similar non-SES risk factors, dementia incidence occurs later among those with more education ¹. In a review paper, Valenzuela and Sachdev found that the majority of cohort studies up to 2004 found a protective effect of education and occupational attainment; the overall odds ratio indicated a 46% decrease in risk for individuals with high cognitive reserve ^{1, 110}. In addition to reduced incidence, individuals with greater cognitive reserve tend to decline more quickly after a diagnosis of dementia compared to individuals with less cognitive reserve. Because those with higher cognitive reserve are able to

buffer dementia pathology, the clinical and behavioral manifestations of the disease occurs later in the disease process. This leads to a faster rate of decline in individuals with greater cognitive reserve (Figure 3). Imaging and other neurophysiological evidence additionally suggest that lower SES and lower cognitive reserve are risk factors for cognitive decline. Higher education was shown to be associated with reduced cerebral blood flow in the parietotemporal areas, implying that patients with greater cognitive reserve could tolerate greater AD pathology ¹¹¹. Other studies since then have utilized positron emission tomography (PET) and fMRI methods to provide evidence for neural reserve, a concept related to changes in neural activity associated with changes in task demand (efficiency), and neural compensation, the use of structures and networks to compensate for pathology and damage ¹¹².

Research imperative

From an epidemiological point of view, in order to reduce prevalence of AD and other major neurocognitive disorders associated with aging, researchers and policy makers should focus on groups that are 1) at high risk for developing the disease and 2) large and growing in number. As summarized above, low SES groups are at higher risk for developing neurocognitive disorders compared to higher SES groups. Additionally, based on the 2012 Current Population Survey by the U.S. Census Bureau, in 2011, 15% of the United States population was below the poverty line and 28% had at least one spell of poverty. Additionally, household income in the United States declined from 2010-2011 and has not yet recovered from pre-2001 recession levels ¹¹³, indicating that the percentage of Americans below the poverty line may not be decreasing. From an economic point of view, researchers should focus on diseases which are the most expensive, particularly to entitlement programs. According to a recent RAND Corporation study, the annual cost of dementia – \$157 billion to \$215 billion - makes the disease the most costly to the nation ¹¹⁴. Additionally, health care costs for approximately 30% of people with AD are covered by both Medicare and Medicaid ⁴; therefore annual costs associated with subsidizing low SES individuals' health care are considerable.

When do we intervene?

With the advent of new technologies and identification of biomarkers that indicate risk for major neurocognitive disorders, researchers can better identify groups of individuals to test preventive

interventions. The three main levels of prevention are primary, secondary, and tertiary. Considering Figure 1, primary prevention, which focuses on individuals at a pre-pathologic stage, would focus on individuals on the normal aging trajectory before pre-clinical decline. Secondary prevention would focus on individuals in the preclinical and MCI stage, prior to clinical symptoms. Finally, tertiary prevention would focus on halting the disease process after clinical symptoms.

Figure 2 indicates that at very early ages, pathology related to major neurocognitive disorders such as AD, may start to accumulate while individuals are cognitively normal ⁴⁷. For example, β -amyloid ($A\beta$) peptide, the first indicator of AD pathology, can accumulate years before any clinical diagnosis ². Therefore, primary prevention for many aging related major neurocognitive disorders would target individuals at an early age. Secondary prevention, in particular selective interventions which target sub-groups (e.g., low SES individuals) at higher than average risk for the disorder ¹¹⁵, would target individuals in the MCI or late preclinical stage who have accumulated AD pathology and may exhibit some decline in cognitive function. Finally, tertiary prevention would focus on symptomatic therapy in individuals who are on a trajectory of irreversible cognitive decline.

Advantages of selected secondary preventive interventions include specificity and efficacy. Selective interventions can be more specific to individuals because they focus on subgroups of the population that are less heterogeneous than the overall population. These subgroups usually share risk characteristics and factors that separate them from the general population; interventions are usually specific to the shared risk factors. Through a clear understanding of risk factors for the disorders, selective interventions have the potential to be the best type of intervention to reduce overall prevalence of the disorder in the general population ¹¹⁵.

For major neurocognitive disorders such as AD, researchers are beginning to have a much clearer understanding of risk factors and biomarkers of pathology. A number of clinical and lifestyle secondary preventive interventions have targeted individuals within the prodromal stage of the disease process with the hope of reducing incidence of neurocognitive disorders. While epidemiological and imaging research (and a few successful exercise interventions) have provided support for the efficacy of physical activity interventions to improve/ maintain cognition, there

are a number of research gaps that need to be addressed in order to move towards the design of an optimal intervention that targets high risk individuals.

Research Gaps

Over the last few decades, physical activity as a protective lifestyle factor has emerged as a significant locus of intervention within the study of aging. As elegantly described by the NIH Cognitive and Emotional Health Project ¹¹⁶, the future of work for researchers dedicated to determining the predictive utility of interventions or factors on cognitive decline/ AD may be in merging the relatively new concepts of “successful aging” with the more traditional field of “normal aging.” Successful aging emphasizes the importance of lifestyle changes ¹¹⁷, a reflection of the paradigm that aging is not a normative and static experience, the trajectory of which one inherits by birth (referring to both underlying genetic fate and static circumstances).

With the advent of new observational technology, including MRI, the possibility of identifying the mechanism for how physical activity affects cognition is possible. Evidence from animal and emerging human models shows that the association may be explained by a number of different mechanisms associated with multiple pathways.

Evidence from animal and emerging human models shows that the mechanism can be explained in part by both trophic and cerebrovascular mechanisms, but how do those mechanisms interact? And how does environmental enrichment (which includes both social and cognitive components) impact the benefits of locomotion? Additionally, are there measurable cognitive benefits from non-exercise, low-intensity, functional physical activities that do not require exercise facilities and environments/ neighborhoods that encourage increased physical activity?

One way to begin to answer these questions is to explore novel interventions that test multi-modal, well- defined activities that tap into key components of aging and test multiple independent and additive pathways. Additionally interventions that utilize objective metrics of physical activity, biomarkers, and sophisticated and documented MRI/fMRI methodologies, can carefully explore potential mechanisms underlying associations.

The following thesis utilizes the Baltimore Experience Corps Trial (BECT) and the Brain Health Study (BHS), a sub-study within BECT, to begin to address the research gaps presented above.

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Chapter 3.

Study overview

Introduction

In 2012, over 60% of U.S. adults 60 years of age and older were retired ¹. Between 2012 and 2050, the percentage of the population over the age of 65 will more than double ², substantially increasing the number of retired adults. This trend indicates the importance of developing and sustaining programs that will increase disability-free years of life for older adults, many of whom will be living over one third of their lives post-retirement.

Public health promotion programs focused on improving health-related behaviors associated with mortality and morbidity typically target three domains of activity: physical, social, and cognitive. Evidence from a number of large-scale epidemiological studies indicates that these activities are each associated with reduced mortality, fewer chronic diseases, improved quality of life, and reduced hospitalization. Physical activity, for example, is associated with lower risk of adverse health outcomes including all-cause mortality ^{3,4}, falls and fractures ⁵, metabolic syndrome ⁶, diabetes ^{7,8}, functional limitations ⁹, and cognitive decline ^{10,11} and dementia¹²⁻¹⁴. While a number of clinical trials have indicated that activity interventions may be beneficial, many older adults have difficulty initiating and adhering to activity programs. This is of particular concern for older adults of low socio-economic status (SES) who, compared to high SES individuals, may have lower baseline levels of activity (particularly physical activity (e.g., ¹⁵) and access to fewer activity-related facilities due to restrictive environment and neighborhood characteristics ¹⁶⁻¹⁹.

Program background and history

Experience Corps (EC) represents a novel approach to older adult health promotion interventions. Developed by Dr. Linda Fried and Marc Freedman, Experience Corps is a high-intensity volunteer civic engagement activity designed to simultaneously benefit older adults and elementary school children ^{20,21}. The program offers intensive service in public schools by engaging older adults in a variety of school-based volunteer activities designed to have a high impact on the success of children through individual and group tutoring in reading and math, library work, and resolving conflict and behavior issues ²⁰. The essential program elements of EC were developed to increase participation and appeal to older adults ^{22,23}, reduce barriers to participate particularly for ethnic minorities and those of low SES ²⁴, and were based on recommendations for promoting activity ²⁵.

²⁶. These elements included: 1) core, intergenerational, generative, and high-impact volunteer roles; 2) a minimum of 15 hours/ week of service during the academic year; 3) a critical mass of volunteers in each school and a team approach to provide social support and reinforcement; 4) training and infrastructure to support effectiveness and retention; 5) reimbursement for expenses; and 6) program flexibility and a diversity of roles to meet the needs and skills of individual volunteers ²⁰.

Experience Corps currently operates in 19 cities across the country and has more than 2,000 volunteer members; since 2011 the service program has been under AARP ²⁷. Experience Corps Baltimore was established in 1998 through a partnership between the Johns Hopkins University Center on Aging and Health and the Greater Homewood Community Corporation (GHCC) ²⁸ and recruited, trained, and placed older adults into volunteer roles serving mostly lower-income children in Title I public elementary schools in Baltimore City. Intergenerational civic engagement programs like EC Baltimore have great potential to impact both older adults and children through sustained and meaningful relationships that may accomplish a range of community and educational goals including increased social capital, reduction of poverty and violence, and a better school climate ^{29, 30}. Particularly in under-resourced urban areas, civic engagement programs may provide needed health benefits to volunteers, and bring a much needed, high-impact volunteer force to schools.

Baltimore City: a brief modern history of the people

Baltimore City has historically been one of the largest cities in the U.S. In 1950, Baltimore City's population was at its peak due to the World War II related economic boom that drove immigration into Baltimore City and established the Inner Harbor as a major port and manufacturing center. According to the U.S. Census, at this time Baltimore City was approximately 24% black and contributed to approximately 75% of Maryland's jobs ³¹. The population and economy of Baltimore have changed significantly over the last six decades. Currently Baltimore has two-thirds of the population it had in 1950, a median household income that is over \$30,000 less than the state median, and a homeownership percentage 30% less than the state percentage. Due to the migration of black Americans from the south into Baltimore City starting in the 19th century and

the migration of white Americans out of Baltimore City into the adjacent counties (i.e., “white flight”), currently Baltimore is 63% black ³².

In the 1900s, black residents in Baltimore City were spread throughout neighborhoods and there were no Black majority neighborhoods. As black southerners began moving into the City, a number of policies were developed by the Baltimore City government to restrict black ownership to specific neighborhoods in the city. This set of policies, also referred to as “red-lining”, led to racially segregated and economically depressed neighborhoods that define many majority black neighborhoods in Baltimore City today ³³. Additionally, more recently the black middle class has started to follow the migration of middle-class white residents into the counties; between 1990-2000, the number of Black residents leaving the city equaled the number of white residents ^{34, 35}. The result is a city that is increasingly poor where many residents rely on low-wage, service industry jobs as their primary source of income ³⁶.

Baltimore City: a brief modern history and a snapshot of the schools

Baltimore City has 188 public schools and programs with a total student enrollment of approximately 85,000 ³⁷. Over the last few decades, public schools in the city are serving an increasing poor and minority community; in 2013, 84% of students enrolled in the City’s schools were low-income and 83% were black ^{37, 38}. The history of the Baltimore City Public School System (BCPSS) is intertwined with the history of the people. In 1952 Baltimore desegregated its school system, and by the mid 1960s was spending approximately 18% less per student per year compared to Baltimore County ³⁸. In the 1980s, BCPSS was ranked 22 out of 24 school districts in Maryland in terms of annual spending per student ³⁹. In the 2000s, approximately 35% of Baltimore’s students received a high school diploma, 12.5% were suspended per year (compared to a nationwide average of 7%) ⁴⁰.

Experience Corps Baltimore: an urban public health intervention

Experience Corps Baltimore was designed to address two significant concerns in Baltimore City: 1) an aging, mostly black, older adult population living in under-resourced neighborhoods in the City and at elevated socio-demographic risk for cognitive and physical function decline; and 2) a

City public school system that is underfunded without the resources and expertise to provide adequate education for its students. The founders of the program designed EC as a social approach to health promotion for older adults that could simultaneously improve the educational outcomes of students ²⁰.

Although minorities and those with low socio-economic status are often disproportionately affected by cognitive and physical function disability ^{41, 42}, they are often unrepresented in epidemiological and clinical research related to addressing risk factors that may positively affect those adverse health outcomes. The result are research findings that may not translate to underserved and underrepresented populations, as well as policy solutions (based on those findings) that also may not be relevant for those populations. A large body of research has explored the barriers and facilitators to participation in clinical research among minorities, which include a lack of awareness, mistrust of researchers, and fear ^{43, 44}. In response, many federal funding agencies have enforced inclusion of a racially diverse population in research studies; however recruitment and retention of these groups continues to be difficult. For health promotion intervention studies, similar barriers exist that limit access to interventions among minority groups. In their paper guiding the adaptation of health interventions for minority groups, Netto et al. identified five principles: “(i) use community resources to publicize the intervention and increase accessibility; (ii) identify and address barriers to access and participation; (iii) develop communication strategies which are sensitive to language use and information requirements; (iv) work with cultural or religious values that either promote or hinder behavioral change; and (v) accommodate varying degrees of cultural identification.” ⁴⁵.

Experience Corps Baltimore was developed to specifically target older adults not traditionally targeted by health promotion programs. The program 1) recruited older adult participants by utilizing resources already available to the target population including health fairs, community organizations, senior housing facilities, and targeted radio stations; 2) recruited older adults based on their desire to be “generative” or give back to their community rather than targeting specific health promoting activities (e.g., physical activity); 3) utilized community members and word of mouth to advertise and promote the intervention; 4) recognized cultural and religious values in choosing the medium of recruitment (e.g., Gospel stations); and 5) developed a broad recruitment message, including highlighting the various volunteering roles available to participants as well as

appealing to participants' interest in the scientific process, designed to appeal to both men and women as well as individuals with varying cultural or religious values^{46, 47}.

The program was also developed to naturally integrate into urban areas. Many neighborhoods in Baltimore City may not be conducive to physical activity (e.g., walking)¹⁶⁻¹⁹, and developing interventions that require infrastructure not already present in neighborhoods or that require individuals to travel extensively outside their neighborhoods, may create barriers to participation. Experience Corps Baltimore relied on public schools that are part of communities and easily accessible to older adults; this was a cost-effective way that leveraged the resources already available within a neighborhood or community.

Study Conceptual Models

The two conceptual models that form the foundation of EC as a health intervention for older adults are generativity and social capital ²¹. Generativity is a concept developed by Eric Erickson that is defined as the transference of knowledge and wisdom to the younger generation ⁴⁸. Experience Corps recruited and retained participants based on the generative motivations of older adults; the health benefits of the program are hypothesized to be achieved through participants enacting these motivations with children within the public school system ⁴⁹.

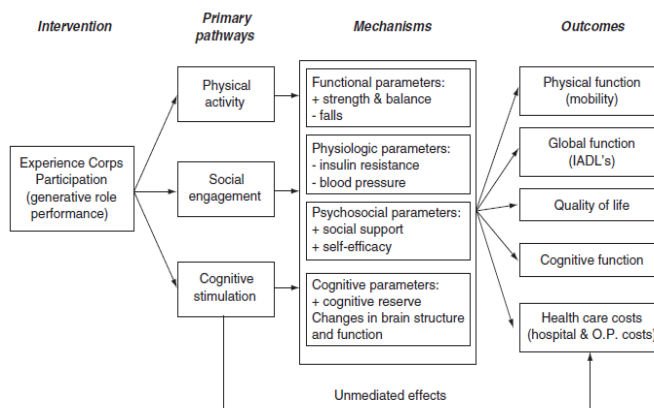


Figure 1: Causal pathways through which Experience Corps Program is hypothesized to benefit the health and functioning of older adults

Social capital is related to the networks of relationships among individuals who share a community that enables that community to function. Experience Corps builds social capital at the individual, school, and community level through the development of close social bonds between volunteers and the community (including students, parents, and caretakers of students

within the community, teachers, and school administrators and staff) ⁵⁰. This is hypothesized to

be a primary vehicle through which the EC program may enhance both individual and public health ²¹.

The program was specifically designed to enhance the physical, cognitive, and social engagement of volunteers (Figure 1). As mentioned previously, prior studies indicate that increasing each of these activities is associated with a reduction in adverse health outcomes. EC has been criticized because it is very difficult to understand the mechanisms that may drive positive outcomes because the intervention cannot be separated out into its parts (what is social activity, cognitive activity, physical activity?). This is a common criticism of real-world interventions. In fact, most activity interventions in humans (e.g. ^{51, 52}) attempt to control for confounding factors (e.g., social activity in a group exercise intervention) by choosing an appropriate control group. However this assumes that the mechanism of benefit of the activity being tested is independent of the confounding factor, and that the confounding factor is similar in the intervention and control group. These are assumptions that are often difficult to test and are very difficult to defend.

One of the strengths of EC is that it is a multimodal intervention ^{20, 53} that combines multiple activity pathways. If we consider EC within the context of physical activity interventions, the program is the first human intervention to test the hypothesis that physical activity within the context of cognitive and social activity may provide cognitive and brain health related benefits. This hypothesis has been tested extensively in animal models. Researchers have coupled exercise (a subtype of physical activity) with environmental enrichment – considered cognitive stimulation through social interactions and novelty – to understand hippocampal neurogenesis. Animal studies have shown the influence of the environment on brain structure and function ⁵⁴, providing some evidence for the importance of complexity and novelty as key stimuli for neuronal development. While animals in their natural environment certainly exhibit a large degree of physical activity, physical activity alone does not seem to explain the effects of the environment ⁵⁵. Kempermann et al. explain that, “In animals, most if not all aspects of cognition are inseparable from locomotion and physical activity. Exploration, spatial navigation, and most types of learning accessible in a rodent are based on its movement in the outer world. Search for food, shelter, and mates are physical activities requiring mental input to be successful on both a phylogenetic and ontogenetic scale” ⁵⁶. They continue to argue that locomotion stimulates and proliferates precursor cells of adult neurons, and environmental enrichment promotes the survival of the

neurons to adulthood. While measuring environmental enrichment (which includes social interactions, novelty, etc.) is difficult particularly in human models, this coupling mechanism provides an elegant explanation for the relationship between physical activity and cognition that extends the cognitive benefits of physical activity beyond aerobic fitness ⁵⁶. Experience Corps offers an opportunity to test this environmental enrichment hypothesis. When considered within this context, formally testing the benefits of EC and exploring the mechanisms of those benefits is an exciting, bold, and ambitious project.

Study background and history

Experience Corps was first implemented across five cities in 1995. In order to formally test the efficacy of EC, in 1999, the Johns Hopkins University and its community partner, the Greater Homewood Community Corporation, developed a one-year pilot randomized trial of EC vs. a control group in Baltimore ²⁰. Those randomized to the control group were referred to the Baltimore City Commission on Aging and Retirement (CARE) where they were offered volunteer opportunities other than EC, and given the option of being placed on a wait-list to participate in EC the following year.

The pilot trial found that EC participants, compared to the control group, had increased physical activity and improved mobility ^{20, 57}, and improved cognitive and brain function ^{58, 59}. Specifically, the pilot trial found that volunteers at low-baseline physical activity significantly increased their self-report physical activity (in kilocalories) at follow-up ⁵⁷, and volunteers reported an increase in their perception of being physically active and the number of stairs climbed per week. Carlson et al. found that volunteers, relative to controls, showed improvements in the executive function cognitive domain; the improvements were most pronounced in volunteers with impaired executive function at baseline ⁵⁸. Using fMRI, Carlson et al. additionally found that volunteers vs. controls exhibited intervention-specific increases in brain activation in the prefrontal cortex (area associated with executive function) and the anterior cingulate cortex, with behavioral improvements in an inhibitory cognitive task ⁵⁹.

In 2006, Johns Hopkins University and the Greater Homewood Community Corporation began recruiting for the Baltimore Experience Corps Trial (BECT), an intention-to-treat, randomized,

controlled effectiveness trial in Baltimore City ⁴⁷. In 2013, Tan et al. reported extensively on this novel, academic-community partnership and how community-based participatory research principles were applied throughout the evolution of the successful partnership ²⁸. Recruitment to the trial has been described extensively ^{46, 53} and included outreach at health fairs and senior housing, mailings to clubs, including AARP, and advertisements on targeted radio stations ⁴⁷. Enrollment criteria included agreeing to accept randomization and if randomized to the intervention, agreeing to serve at least 15 hours per week for a full school year (with the option of continuing for an additional year) at a designated school. Additional criteria included: aged \geq 60 years, \geq 24 on the Mini-Mental State Exam (MMSE) ⁶⁰, and ability to read at a minimum 6th grade level ⁶¹. The cognitive and literacy criteria were to ensure that participants would be able to assist teachers and children in a safe and helpful manner. Finally participants had to agree to and pass a criminal background check mandated and conducted by the Baltimore Public School System ⁴⁷.

Prior to randomization to the BECT, participants were offered simultaneous enrollment in the Brain Health Study (BHS), a sub-study nested within the larger trial ^{62, 63}. The BHS was designed by Dr. Carlson to better understand the biological mechanisms of cognitive and brain plasticity; additional measures collected within the BHS, including objective physical activity metrics and structural and functional magnetic resonance imaging, serve as both intermediary biomarkers that may explain the mechanisms underlying outcomes of the overall trial, as well as independent outcomes used to explore intervention-related effects. Additional enrollment criteria for the BHS included: right hand dominance to avoid possible confounds due to laterality in left-handed individuals, no history of atrial fibrillation, stroke, brain tumor, or brain surgery for a cerebral aneurism, and free of a pace-maker or any ferrous metal objects in the body ⁵⁹.

For the BECT, data were collected by trained evaluators at baseline, and 4, 8, 12, 16, 20, and 24 month follow-up evaluations. Extensive in-person evaluations were conducted at baseline and annual follow-ups (12 and 24 month). BHS data were collected approximately concurrently with BECT data at baseline and 12 and 24 month follow-up evaluations. Data collected for the BECT included demographic data, overall trial outcome data (mobility disability, falls, and functional data), physical health data (e.g., self-report physical activity), behavioral cognitive measures (e.g., tests of psychomotor speed, visuo-spatial memory, verbal memory, executive function),

performance measures (e.g., grip strength, walking speed), and psychosocial measures (e.g., perceived SES, geriatric depression scale) ⁴⁷. Data collected for the BHS included fMRI and MRI data (e.g., region specific brain activation, hippocampal volume), objective physical activity data, fasting blood data (e.g., metabolic and lipid panel), cortisol data, additional cognitive measures (e.g., tests of executive function and psychomotor speed), and additional psychosocial questionnaires. All baseline data were collected prior to randomization to ensure that the intervention had no effects on the results. The study protocol was approved by the Johns Hopkins School of Medicine Institutional Review Board and each participant provided written, informed consent.

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Chapter 4.

Description of primary measure

Introduction

The step activity monitor (SAM; Orthocare Innovations, Mt. Terrace, WA) is a pager-sized microprocessor-linked accelerometer with adjustable filtering thresholds that continuously measures step activity. The SAM measures the number of steps at one-minute intervals using acceleration, position and timing information, and therefore can be used to understand patterns of physical activity that occur across the day versus a summary of daily activity typically provided by standard pedometers. The SAM can also be used to differentiate between low-intensity and moderate- to vigorous-intensity walking activity as well as measure and characterize components of physical activity including amount, duration, and frequency ^{1, 2}. The SAM has been validated across a range of community-dwelling older adult samples with varying functional limitations using self-report and objective measures (e.g., hand-tallied step counts and other accelerometers) ³⁻⁵. The SAM is particularly sensitive in measuring activity at decreased gait speeds ⁴, and is well tolerated by older adults because it is small (pager sized) and placed on the ankle vs. the hip ⁶.

The SAM specifically measures walking activity, which is a component of all total physical activity, or all activities that require energy expenditure above rest. The SAM is placed on the ankle (vs. the hip), which additionally increases the accuracy of measured walking activity. There are at least two biases that must be considered when using walking activity as the primary measure of physical activity and using the SAM to measure that activity. First, walking activity excludes movement associated with trunk and upper body activities. This should not pose a problem if we believe that those movements are correlated strongly with walking activity across the population being measured. However, non-ambulatory activities that require the trunk and upper body (e.g., knitting, cooking while sitting, and other very low-intensity activities) will be excluded from the walking activity measure. If the percentage of non-ambulatory activity and the correlation between trunk and upper body activities, and walking activity varies significantly across the population being studied, this bias – unless controlled for – may affect results. Second, the smallest unit of measurement provided by the SAM is a step. All metrics generated from the SAM therefore require the assumption that a step is equivalent across all individuals within the population being studied. Within the context of physical activity measurement, this assumption can be restated as: the energy cost or MET of each step is assumed to be equivalent across all individuals. This assumption may be violated in a number of scenarios. Weight bearing activities,

for example, increase the METs/step and cannot be discriminated by the SAM. Additionally, stride length and variability, which are related to steps and gait, are associated with height and weight⁷. Controlling for these parameters may be possible by averaging the relationship between the two variables of interest across values of the confounder (e.g., adding the confounder as a covariate in a linear regression model). However, a careful consideration of the causal model being tested is essential. For many of the biases described above, the confounder may be unmeasured and therefore results must be explicitly described within the context of the potential biases.

SAM: Data collection

The SAM was included in baseline, 12-month, and 24-month evaluations for all participants within the BHS. At baseline, additional BECT participants from a physical activity sub-study were included in data collection. At evaluations, the SAM was attached to the participant's dominant ankle and calibrated by comparing hand-tallied step counts to one minute of walking activity at the participant's normal gait. Participants in the BHS were instructed to wear the SAM for three days; this data collection period was extended to 7 days for the physical activity substudy. Participants were instructed to wear the SAM for the entire data collection period, and remove the device only when bathing, showering, or swimming, and to replace the device immediately after. Participants were additionally instructed to keep a wear time /activity diary at approximately one-hour intervals throughout these days. After the completion of data collection, participants were instructed to mail back, in a pre-stamped, addressed envelope, the SAM and activity diary. The majority of participants wore the SAM during the late summer and early fall, which reduced the influence of seasonal effects.

There are three important variables that need to be considered when collecting objective physical activity data: 1) Device type and body placement; 2) Optimal number of days of data collection^{††}; and 3) biases due to temporal trends in physical activity. Device type and body placement have been described above; see^{8,9} for additional information on optimal placement for the detection

^{††} Optimal number of hours/day of data collection, or minimum daily wear time, is also an important consideration. For older adults who are sedentary, it is particularly difficult to discriminate between sedentary days vs. non compliant days as well as sedentary hours vs non-compliant hours. This is discussed in the section, *SAM: Data processing*.

of everyday activities. The overall goal of determining the optimal activity collection period and identifying potential temporal trends in activity is to generate physical activity data that are representative of the physical activity level of an individual at a particular time point. Many studies of community-dwelling older adults assume that acute medical events do not occur during the data collection period, and physical activity is generally stable trait over some period of time greater than the period of time chosen for data collection. A physical activity researcher's goal is to collect enough data in order to assure that the data are representative of an individual's "regular" physical activity while at the same time not overburdening the participant and adversely affecting compliance and fidelity of data collection.

A number of research papers have explored the question of what is the appropriate total number of days of data collection necessary to reliably assess physical activity using an accelerometer in older adults ^{10, 11}. The general consensus is that 3-5 days should be appropriate; however, due to weekly temporal trends (described below), 7 days is optimal ¹¹. These approximations can vary depending on specific demographics of the population (e.g., gender, chronic conditions, mobility). Generally, younger populations seem to require more days of data collection in order to reliably estimate physical activity compared to older populations ¹².

The two temporal trends that need to be considered when collecting objective physical activity are weekday versus weekend differences and seasonal differences. Generally for individuals employed or in school from Monday to Friday, there may be differences in activity during the week versus on the standard weekend days (Saturday and Sunday) and therefore in order to reliability collect physical activity at least one weekend day should be included in data collection ^{13, 14}. When collecting data among lower-income individuals employed in the service-industry, underemployed, or working multiple jobs, days off may not be consecutive (if at all) and may not fall on Saturday and Sunday. For older adults who may be retired, underemployed, or volunteering, differences among weekdays as well as differences between weekdays and weekends may be unclear. Understanding seasonal variations may also be difficult depending on the population. Although intuition suggests that individuals may be more active during warmer and dryer seasons vs. colder and rainy seasons, prior research indicates that the seasonal effect is unclear in children ¹⁵, and adults ^{16, 17}. Similar again to weekday versus weekend effects, the effect can vary across individuals depending on demographic characteristics. Unless specific

questions are asked in order to understand temporal trends, it may be difficult to control for these trends particularly in “non-normative” (when considering the field of physical activity research) populations.

SAM: Data processing

The SAM records stride counts, or the number of steps walked on the leg attached to the SAM, within each minute of each 24-hour period prior between when the administrator/ evaluator programs the SAM and then after data collection, places the SAM on the dock, and accesses the data from the device. Figure 1 indicates the sequence of steps for data collection and processing of SAM data. The SAM was first programmed and attached to the participant’s dominant ankle at the end of the evaluation, which occurred at approximately mid-day at the Kennedy Krieger Institute on the Johns Hopkins Medical Campus or, in the case of the physical activity sub-study, the Charles Street offices in Baltimore used by BECT staff. The participant was then instructed to wear the SAM and then send it back to the BECT offices via FedEx. After receiving the SAM after the data collection period, the administrator then read and saved the data, indicating the participant’s id and visit number as the file name. Files were first downloaded in .swb format (proprietary format developed by device manufacturers), converted to excel using the software’s outsheet command, converted to a text file, and inputted into Stata version 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP). Each participant’s raw data consisted of 1440 rows (number of steps per minute per day) and a column for each day of data collection between programming and data download. Raw data were modified to an analyzable format, and all participant data were merged into a final raw data file.

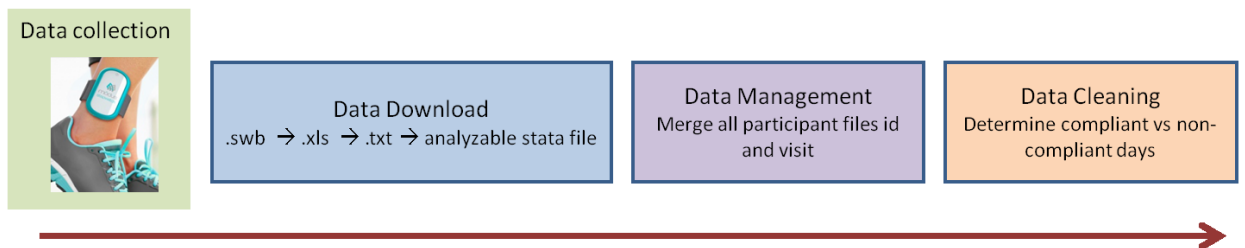


Figure 1. Sequence of steps for data collection and processing of Step Activity Monitor (SAM) data

Each participant’s dataset included the following types of data: 1) day 1: half day when the SAM was first programmed and placed on the participant’s ankle; 2) full days when the participant was

compliant with data collection protocol; 3) days when the participant was not compliant with data collection protocol; and 4) days between the completion of data collection protocol and administrator receipt of the device (e.g., FedEx transit time). Data cleaning was completed in order to only include full days when the participant was compliant with data collection protocol. We excluded all other days, including non-compliant days, according to the following five criteria: 1) day 1 (the half day when the SAM was first programmed); 2) days with less than 201 total steps/day; 3) days with less than a total of six hours of any activity between wake and sleep times; 4) days with six consecutive hours of inactivity (< 1 step) between wake and sleep times¹⁸; and 5) days when participants recorded not following data collection protocol in their activity diaries. Wake and sleep times and recorded noncompliance were determined using the activity diary that participants completed during the data collection period. If diary information was not available for wake and sleep times, we determined wake and sleep times using the Pittsburgh Sleep Activity Questionnaire, which recorded wake and sleep times “during the past month”¹⁹, or imputed using the group’s average wake and sleep times.

Data cleaning for accelerometer data is typically done to exclude noncompliant days in order to generate data that are representative of participants’ physical activity. Although analysts are usually concerned with incorrectly including days that will artificially underestimate average physical activity, there are a few scenarios^{††} where an accelerometer may overestimate activity: 1) spurious data due to hardware/ software malfunctions; and 2) certain activities that may overestimate physical activity due to device specific hardware/ software. Spurious data include data that are not biologically plausible; accelerometer data cleaning protocol typically removes these data by applying an upper-threshold filter²⁰. For certain devices (e.g., pedometers and some accelerometers), non-ambulatory activities such as biking and travelling in a car can artificially produce overestimates of either steps walked (pedometer) or acceleration (accelerometer). In tri-axial accelerometers, the magnitude of acceleration is relative to other axes and therefore the acceleration of the vehicle (e.g. a car’s accelerative force) will not produce an accelerative force and resulting voltage in the accelerometer; however as an individual moves within a car due to bumps in the road, curves, etc., a voltage will register that is an overestimate

^{††} These scenarios do not include the use of proprietary metrics that are developed by accelerometer manufacturers including caloric expenditure. The algorithms used to generate these metrics are often flawed and may underestimate or overestimate true caloric expenditure.

of the individual's actual physical activity. While many pedometers have sensors to filter "false steps," the resulting false steps generated from non-ambulatory activities including biking and swimming are difficult to interpret (e.g., ²¹). Finally, overestimation can also occur due to an incorrect sampling frame where the data collected accurately reflects an individual's true physical activity on a given day; however, that day is not representative. Adjusting data collection protocols by increasing the total number of days may correct for this.

In order to exclude non-compliant days, researchers typically develop a model of the characteristics of a non-compliant day specific to the population being studied, and then write a program that will identify those days based on the model, and exclude them from the final dataset. Although some studies, including ours, use multiple methods to clean the data – e.g., combining data driven methodologies with participant's self-report of non-compliance – the majority of large epidemiological studies using accelerometers rely solely on non-compliant models to clean data. A number of studies have identified optimal cleaning protocols for non-compliant days. Masse et al. compared the effect of four different data cleaning algorithms on assessing physical activity within a population. The algorithms varied by: 1) definition of a "wear" period; 2) minimal "wear" requirement to constitute a compliant day; and 3) identifying spurious data ¹⁸. A wear period is defined as a period of time where the accelerometer registers a non-zero value over the epoch length of data collection (e.g., every 5 seconds, every min, etc.^{§§}); a non-wear period is a string of zeros over a period of time defined by the researcher. In our SAM protocol, we defined non-wear time as a string of zeros over one hour. We used a rolling window to define non-wear time where each time a zero was encountered over the 1440 minute day, the count would restart. The minimal "wear" requirement is typically defined as the percentage of the waking day where the participant is identified as wearing the device (wear time). Typically studies estimate the waking day as 12 hours ¹⁸. Thresholds for spurious data are population and device specific. These thresholds are rarely provided by device manufacturers and often vary across studies.

^{§§} Epoch lengths are typically one minute (leading to 1440 measurements/day). This may not be the optimal measurement period; for example in children where bouts of activity may be sporadic and short, a one minute epoch length may underestimate physical activity. Newer accelerometers allow researchers to choose the epoch length; the GENEActiv accelerometer, for example, allows the user to choose various sampling frequencies (10-100 Hertz).

One of the primary difficulties, particularly in research studies involving sedentary populations including older adults with a high number of chronic conditions and mobility limitations, is discerning between sedentary time and non-compliance. This is an extremely important issue because decisions on data cleaning can profoundly affect results. Generally, criteria to define a wear or non-wear period should accommodate the characteristics of the population. A non-wear hour during waking time in a younger and mobile population can be defined as 60 minutes of consecutive non-zeros with less than 2 interruptions of any activity, whereas a non-wear hour in an older population can be defined as 60 minutes of consecutive non-zeros with no interruptions. The more conservative criteria to exclude interruptions in the older adult population allow for minimally active hours to be considered sedentary (and included in the final dataset) rather than non-compliant. Alternatively, the period of consecutive zeros considered to be non-wear can be varied to accommodate the specific population; shorter periods for younger participants and longer periods for older participants ^{22, 23}.

SAM: metrics

The SAM can be used measure categorical variables, including characterizing the proportion of a particular population that meets physical activity guidelines ^{24, 25}. The SAM can additionally measure the intensity of walking activity, including low-, moderate-, and vigorous-intensity ^{26, 27}. Finally, the SAM can be used to calculate metrics representing components of daily activity, including amount (total steps/day), duration (minutes/day of step activity), and bouts (consecutive minutes of activity within a predefined interval) ^{1, 2}.

In order to characterize the proportion of participants meeting physical activity guidelines a threshold of 10,000 steps/day developed in previous studies may be a reasonable equivalent of U.S. physical activity guidelines ^{24, 25}. Participants who walk an average of < 10,000 steps/day may be classified as less active and $\geq 10,000$ steps/day as active. Additionally, based on previous studies translating physical activity recommendations (30 minutes of moderate-intensity activity/day (MVPA) that can be split into three, 10-minute bouts/day) into a pedometer-based step goal (three bouts/day of 1000 steps in 10 minutes) ^{26, 27}, participants who complete < three bouts/day on average may be classified as less active, and \geq three bouts/day as active. This guideline is based on studies translating laboratory measurements of

oxygen consumption while walking into pedometer-based metrics ^{26, 27}, where low-intensity is defined as a step activity between 0 and 100 steps/min, and moderate- to vigorous-intensity is defined as step activity greater than or equal to 100 steps/min.

In our study protocol we considered both guidelines to characterize the percentage of participants meeting physical activity guidelines. It is important to note that these physical activity guidelines, particularly the 10,000 steps/day threshold, are approximate and should not be considered perfect estimates of U.S physical activity guidelines. In fact, appropriate estimates for “how many steps/day are appropriate?” vary, and the 10,000 steps/day guideline has been driven more by commercial products and organizations than more authoritative research-based groups. Tudor-Locke et al., for example, estimated that 7,000-10,000 steps/day may be equivalent to 30 minutes of daily moderate- to vigorous-intensity physical activity (MVPA; approximate U.S physical activity guidelines) ²⁸; Rowe et al. reported that the 10,000 steps/day threshold may have high accuracy for those who do not achieve 30 minutes of MVPA but low accuracy for those who do achieve 30 minutes of MVPA, and 7,000 to 8,000 steps/day may be a more appropriate threshold or guideline for older adults ²⁹. Overall, 3000 steps in 30 minutes, or 1000 steps over 10 minutes, three times/day is the closest pedometer-based recommendation equivalent to U.S. physical activity guidelines, and measuring total steps/day independent of intensity does not clearly indicate whether an individual meets or doesn’t meet guidelines (see Aoyagi and Shephard’s review of the association between steps/day and number of minutes of MVPA ³⁰). Currently, there is minimal evidence to indicate a specific moderate-intensity cadence (steps/min) for older adults ²⁸. However, the 100 steps/min cadence is often used, and is more informative of moderate-intensity walking activity than the 10,000 steps/day guideline.

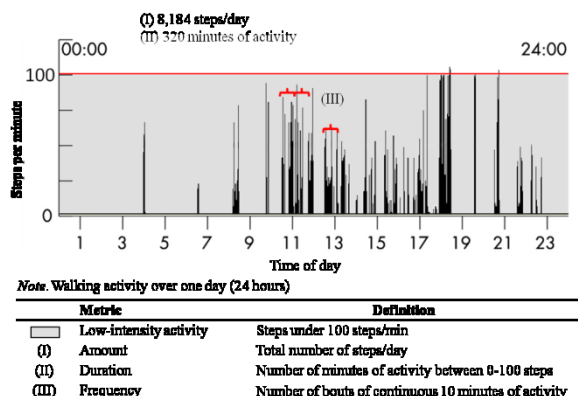


Figure 2: Metrics representing components of activity

Metrics representing components of activity are summarized in Figure 2. All metrics can be divided into low-intensity (> 0 and <100 steps/min) and moderate- to vigorous-intensity (≥ 100 steps/min). Activity amount is defined as the number of steps/day. Activity duration is defined as the number of minutes/day of any activity (>0 steps/min). Activity frequency is

defined as the number of bouts/day of 10-minute activity, and can be calculated by adding the number of times participants complete 10 or 30 consecutive minutes of any activity. This metric is based on U.S. Department of Health and Human Services physical activity recommendations stating that 30-minute bouts of activity can be obtained through three, 10-minute bouts that can be accumulated over the course of the day ^{31, 32}.

Typically, epidemiologic research using objective physical activity data compresses diurnal physical activity data into daily averages in order to understand the volume of physical activity completed/day ³³⁻³⁶. Volume of physical activity/ day measured by the SAM and used in our study protocol is total steps/day; for other accelerometers, volume is either total counts/day or the total magnitude of acceleration at each epoch over the course of the day. This can be considered the area under a typical diurnal, physical activity curve and can be calculated using a simple integral.

$$\int_1^t x \frac{dy}{dx}$$

For activity measured by the SAM, 'x' in the above equation represents steps and 't' is 1440, representing 1440 total minutes in one day. The time dimension is lost in this type of analysis, and components of

physical activity, including amount, are incorporated into one measure. Determining whether or not individuals accomplish physical activity guidelines further compresses the data into a categorical variable of Yes or No. It is possible, however, to consider the time dimension when using pedometers and accelerometers that provides the user with activity over time intervals less than a day. For example, Figure 3 depicts the diurnal pattern of physical activity measured by the SAM for a subset of the BECT. Diurnal patterns have been separated by age quartiles (61.2 (green), 64.0 (red), 67.4 (blue), 75.1 (orange)) in order to show differences in physical activity over a 24-hour period. This graphical representation can be used for other accelerometer data (e.g., analyses using the Actiheart accelerometer in the Baltimore Longitudinal Study of Aging ³⁷), and differences in walking or physical activity by time of day between groups can be explored.

Choosing the appropriate physical activity metric is dependent on the analytic question. For example, in order to better understand population trends and adherence to guidelines, total

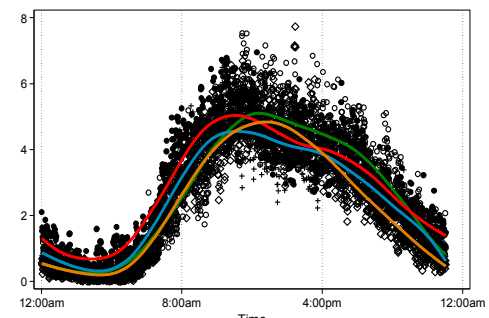


Figure 3: Diurnal pattern of walking activity in the BECT comparing age quartiles

volume of physical activity or whether or not individuals achieve physical activity guidelines may be most important (e.g., ³⁵). Fractionalization of total volume of physical activity into components ¹, may be important, for example, when considering the differential benefits of amount of physical activity depending on intensity (i.e., low-, and moderate- to vigorous-intensity). While activity guidelines were developed based on research indicating the health benefits of moderate- and vigorous-intensity physical activity, recent research using sensitive physical activity measurement devices, including accelerometers, indicates that low-intensity activity which may include non-exercise, leisure-time activities (walking for pleasure), instrumental activities of daily living (e.g., walking related to housework or shopping), as well as low-intensity exercise, may also yield health benefits ^{32, 36, 38-46} ***. In our study protocol, we considered metrics that characterized the physical activity levels of our study population as well as metrics that allowed us to understand the differential benefits of physical activity by intensity.

*** Sedentary behavior (or inactivity) may also be a predictor of health outcomes independent from activity (see Katmarzyk PT. Physical activity sedentary behavior, and health: paradigm paralysis or paradigm shift. *Diabetes* 2010; and Voss et al. Revenge of the “sit” II: Does lifestyle impact neuronal and cognitive health through distinct mechanisms associated with sedentary behavior and physical activity? *Mental Health and Physical Activity* 2014.)

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Chapter 5.

Aim 1: Association between physical activity and physical and cognitive function/ brain health

Introduction

Regular physical activity is a Healthy People 2020 objective for all age groups ¹. More active compared to less active older adults, have lower risk of adverse health outcomes including all-cause mortality ^{2,3}, falls and fractures ⁴, metabolic syndrome ⁵, diabetes ^{6,7}, functional limitations ⁸, physical function ⁹, and cognitive decline ^{10,11} and dementia¹²⁻¹⁴. The epidemiologic evidence for the relationship between physical activity and health has accrued over the past seven decades ¹⁵. Evidence for the relationship between physical activity and cognition specifically is relatively recent. The first, large-scale longitudinal epidemiologic study to show a relationship between late-life physical activity and cognitive aging was the MacArthur Studies of Successful Aging in 1996 ¹⁶. Since then, a number of studies have reported the relationship between increased physical activity and reduced risk of AD ^{12-14, 17} as well as increased physical activity and cognitive health ^{10, 18-21}. In 2008, the Cochrane Review published a review including 11 randomized clinical trials of aerobic physical activity programs and concluded that there was evidence for the benefit of aerobic physical activity on cognitive function ²².

In 1996, the US Surgeon General first developed physical activity guidelines for Americans of all ages ²³. This report was followed up in 2008 by the Physical Activity Guidelines Advisory Committee Report that stated that healthy adults “need moderate-intensity aerobic (endurance) physical activity for a minimum of 30 minutes on five days each week or vigorous-intensity aerobic physical activity for a minimum of 20 minutes on three days each week” ²⁴⁻²⁶. These guidelines cover all adults, including older adults over the age of 60 years, and were developed based on evidence indicating that aerobic activities at moderate or greater intensity drive improved health outcomes.

According to recent CDC surveillance data, less than 16 percent of older adults meet these activity guidelines, and over 30 percent are inactive (report no leisure-time physical activity) ²⁷. Evidence suggests that many older adults have difficulty initiating and adhering to exercise programs ²⁸⁻³¹. This is of particular concern for older adults of low socio-economic status (SES) who have lower baseline physical activity levels than higher SES older adults ^{26, 32, 33}, and fewer physical activity-related facilities due to restrictive environmental and neighborhood characteristics ³⁴⁻³⁶.

While the current physical activity guidelines focus on moderate-intensity to vigorous aerobic physical activities, some studies suggest that low-intensity activity, which may include non-exercise, leisure-time activities (walking for pleasure), instrumental activities of daily living (e.g., walking related to housework or shopping), as well as low-intensity exercise may also yield health benefits ^{26, 37-43}. One of the reasons why guidelines focus on moderate- to vigorous-intensity physical activity may have to do with measurement. Individuals generally are able to recall moderate to vigorous intensity activities (including exercise) better than low-intensity activities (including housework, walking for errands, etc.) ^{44, 45}. As argued by Lee and Shiroma, low-intensity physical activity is not included in guidelines not because it may not be sufficient to drive health benefits, rather the measurement limitations of self-report physical activity questionnaires used in large-scale epidemiologic studies that underlie national guidelines ⁴⁶.

For older adults in particular, understanding the benefits of low-intensity physical activity is essential because the majority of their activity is within the low-intensity range and a large percent report no moderate to vigorous-intensity activity ^{27, 47-49}. However, currently there is limited evidence for the relationship between low-intensity activity and health ⁵⁰⁻⁵². The most recent U.S. Department of Health and Human Services Physical Activity Guidelines recommended additional observational and experimental studies to evaluate the nature of the benefits of low-intensity activity, particularly within understudied populations ²⁶. In the last two decades, self-reported measures have been adapted to specific groups in order to detect the types and frequency of physical activities with better reliability and validity. Additionally, objective measures of physical activity have become more widely used in epidemiologic and other health research allowing for researchers to better measure and understand the health benefits of physical activity broadly, including low-intensity physical activity.

In this study, we describe and characterize physical activity using both self-report and objective measures in a cohort of urban-dwelling older adults at elevated risk for functional decline and disability due to age, low income, low education, and a high number of chronic disease ^{53, 54}. We additionally examine metrics of physical activity and their cross-sectional associations with physical and cognitive health and function. We specifically explore physical activity and cognitive/brain measures within a sex-stratified sample based on prior research from exercise trials on sex

differences ⁵⁵⁻⁵⁷ as well as significant sex differences in physical activity ^{58, 59} and cognition ⁶⁰ among older adults.

We report on baseline physical activity measured using the Community Health Activities Model Program for Seniors (CHAMPS) questionnaire, and daily walking activity measured using an objective step activity monitor (SAM). We hypothesized that 1) the majority of participants would not meet activity guidelines, completing minimal moderate-intensity walking activity; 2) greater low-intensity physical activity, independent of moderate- to vigorous-intensity activity, would be associated with better health across physical function and cognitive function/ brain health measures.

Methods

Participants

The BECT is a randomized, controlled trial funded by the National Institute on Aging to evaluate the health benefits for older adults participating in Experience Corps Baltimore vs. a control group offered other low-service volunteer opportunities. Experience Corps is a high-intensity senior service program designed to place volunteers in elementary schools to improve the academic success of young children. Study design, sampling methodology, and recruitment have been described previously ^{61, 62}. Enrollment criteria included: aged ≥ 60 years, ≥ 24 on the Mini-Mental State Exam (MMSE) ⁶³, and ability to read at a minimum 6th grade level ⁶⁴. Participants agreed to serve 15 or more hours/week for a full school year if randomized to EC. There were no exclusion criteria related to physical activity or physical function, including body mass index (BMI), chronic diseases, or disability. A sub-set of participants were from the Brain Health Study (BHS), a sub-study within the BECT. BHS enrollment criteria have been described previously ^{65, 66}, and included right-hand dominance; free of a pacemaker or other ferrous metals in the body; and no history of brain cancer or brain aneurism/ stroke in the past year. The BHS over sampled for men in order to allow for sex-stratification in analyses ³². A subset of participants including both BHS and BECT were simultaneously offered the SAM. All baseline measurements were taken prior to randomization to ensure that the intervention had no effects on the results. The study protocol

was approved by the Johns Hopkins School of Medicine Institutional Review Board, and each participant provided written, informed consent.

Physical activity measure: SAM protocol

The SAM is a microprocessor-linked sensor that is worn on the dominant ankle and continuously measures step activity in daily life. The device measures the number of steps at one-minute intervals using acceleration, position, and timing information, and can therefore be used to differentiate between low-intensity and moderate to vigorous-intensity walking activity as well as characterize the amount, duration, and frequency of daily walking activity. The SAM has been validated across a range of community-dwelling older adult samples with varying functional limitations using self-report and objective measures (e.g., hand-tallied step counts and accelerometers) ⁶⁹⁻⁷¹. The SAM is particularly sensitive in measuring activity at decreased gait speeds ⁷⁰, and is well tolerated by older adults because it is small and placed on the ankle vs. the hip ⁷². The SAM, which is enclosed within a lightweight, pager-sized plastic case, was attached to the participant's right ankle and calibrated at the baseline evaluation by comparing hand-tallied step counts to one minute of walking activity at the participant's usual gait. We instructed participants to wear the SAM for three to seven days (excluding the first half day of data collection at the study visit when the SAM was placed on the participant's ankle) while keeping a wear time/activity diary at approximately one-hour intervals throughout these days. Participants were instructed to remove the SAM only when bathing, showering, or swimming, and to replace the device immediately after. At the end of this period, participants were asked to mail back, in a pre-stamped, addressed envelope, the SAM, activity diary, and the Pittsburgh Sleep Quality Index (PSQI), which recorded wake and sleep times "during the past month" ⁷³. The majority of participants wore the SAM during late summer and early fall, which reduced the influence of seasonal effects.

The SAM recorded stride counts within each 24-hour period producing 1440, one-minute intervals. We doubled stride counts to reflect step counts for both legs. If diary information was not available, we determined wake and sleep times using the PSQI, or imputed using the group's average wake and sleep times over available days.

We excluded days representing non-compliance according to the following four criteria: 1) less than 201 total steps/day; 2) days with less than a total of six hours of any activity between wake and sleep times; 3) days with six consecutive hours of inactivity (< 1 step) between wake and sleep times⁷⁴; and 4) days when participants recorded not following data collection protocol in their activity diaries. We conservatively elected not to identify and impute missing data (non-wear time) for days included in the analysis⁷⁵.

Of the 702 BECT participants, a subset of 195 were offered the SAM at baseline. Participants provided an average of 4.9 days of data. Based on the exclusion protocol detailed above, an average of 0.8 days (16.4% of data collected) were removed from analysis. Data for eight participants were excluded due to non-compliance, and a total of 187 participants comprised the final sample providing an average of 4.3 days (range: 1-9) each.

Physical activity measure: SAM metrics

In order to characterize the proportion of participants meeting physical activity guidelines within our sample, we used the threshold of 10,000 steps/day developed in previous studies as a reasonable equivalent of U.S. physical activity guidelines^{76, 77}. We classified participants who walked an average of $< 10,000$ steps/day as less active and $\geq 10,000$ steps/day as active. Based on previous studies translating physical activity recommendations (30 minutes of moderate-intensity activity/day that can be split into three, 10-minute bouts/day) into a pedometer-based step goal (three bouts/day of 1000 steps in 10 minutes)^{78, 79}, we additionally classified participants who completed < 3 bouts/day on average as less active, and ≥ 3 bouts/day as active.

Intensity ranges (effort associated with walking) included low-intensity (> 0 steps/min and < 100 steps/min) and moderate to vigorous-intensity (≥ 100 steps/min) based on studies translating laboratory measurements of oxygen consumption while walking into pedometer-based metrics^{78, 79}. Activity amount was defined as the number of steps/day, and was separated into two categories, or types, of activities: 1) low-intensity; and 2) moderate- to vigorous-intensity. Low-intensity included all steps at > 0 steps/min and < 100 steps/min. Steps at ≥ 100 steps/min were excluded from all low-intensity metrics. Moderate- to vigorous-intensity included all steps at

≥100 steps/min. Steps at <100 steps/min were excluded for all moderate- to vigorous-intensity metrics.

Physical activity measure: CHAMPS protocol

The CHAMPS questionnaire ⁶⁷ was developed in order to more sensitively measure variability among mostly underactive older adults by focusing on activities in the low-intensity range that may not be detected by commonly used questionnaires (e.g., Minnesota Leisure Time Physical Activity Questionnaire (MLTA)) that focus more on moderate- to vigorous-intensity physical activities. Several conceptual and methodological issues were considered when developing the CHAMPS, including 1) appropriate assessment of type, amount, and frequency of physical activities; 2) designing questions and methods that will facilitate accurate measurement; 3) minimizing socially desirable responses and 4) enhancing sensitivity to change.

The CHAMPS questionnaire was administered to all BECT participants at baseline by a trained evaluator in person during the baseline assessment. Participants were asked whether they participated in a range of physical activities in the past four weeks; for activities that participants engaged in, frequency of participation (times/week) and total hours (hours/ week) were assessed. The CHAMPS questionnaire assigns older adult specific metabolic equivalent (MET) values, or the energy cost, to each physical activity. The questionnaire therefore is able to distinguish activities by intensity. Low-intensity physical activities assessed by the CHAMPS included light housework around the house, and vigorous-intensity physical activities included jogging and running for exercise.

Participants with missing data for >20% of the activities within the metrics calculated from the CHAMPS questionnaire (described below) were excluded. Of the 702 BECT participants, a range of 1-8 participants, depending on the specific metric, were excluded. The total sample size ranged from 694-701.

Physical activity measure: CHAMPS metrics

In order to characterize the proportion of participants meeting physical activity guidelines within our sample, we used the U.S. physical activity guideline threshold of 150 minutes of moderate-intensity physical activity/ week ²⁶. Based on CHAMPS protocol developed by Stewart et al., ⁶⁷ we determined adherence by calculating the number of minutes/week of physical activities with MET values ≥ 3.0 completed by participants. We estimated minutes/week by multiplying the midpoint of each category of hours/week by 60 ⁶⁸.

The CHAMPS questionnaire allows researchers to calculate caloric expenditure/week of physical activities. Using the American College of Sports Medicine formula (Table A1 of ⁶⁷), caloric expenditure was calculated by multiplying hours/week of each activity by the corresponding MET value, by 3.5, and by body weight in kg/200. We separated this metric into two categories, or types, of activities: 1) low-intensity; and 2) moderate- to vigorous-intensity. Low-intensity physical activities included all activities assigned < 3.0 METs, and moderate- to vigorous intensity physical activities included all activities assigned ≥ 3.0 METs.

Health measures: physical function

We explored the associations between physical activity and physical function measures including mobility and performance-based lower extremity function.

Mobility

Self-reported mobility included difficulty going up and down a flight of stairs (indoors) ^{85, 86}. Participants self-reported 'None', 'A little', 'Some', 'Quite a lot', or 'Cannot do'. Similar to previous studies, the mobility measure was coded as a binary indicator so that odds ratios indicated any self-reported limitation ('A little', 'Some', 'Quite a lot', 'Cannot do') versus no limitation ('None'). This questionnaire was administered to all participants in the BECT.

Performance-based lower extremity function

Performance-based lower extremity function was measured using the short physical performance battery (SPPB). The SPPB assessed walking (timed four-meter walk at the participant's usual pace), tests of balance (ability to stand in the side-by-side, semi-tandem, and tandem positions for 10 seconds), and strength (time to rise from a chair five times) ⁸⁷. We explored the relationship

between physical activity and individual measures of lower-extremity strength as well as the SPPB summary score calculated as follows: for each test, participants received a score of 0-4; zero indicated an inability to complete the test and 4 indicated the highest level of performance. Scores for all three performance-based measures were summed to create a total summary score ranging from zero to 12, with higher scores reflecting better lower-extremity function⁸⁷. We explored the following individual measures: usual and rapid gait speed, and time to complete chair stands. All physical function measures were administered to all participants in the BECT.

Health measures: cognitive function/ brain health

We explored the associations between physical activity and behavioral and structural measures of cognitive function/ brain health. Behavioral measures were within the following cognitive domains: global cognition, executive function, memory, and processing speed. Structural measures included hippocampal and thalamus volume.

Global Cognition

Global cognition is a measure of cognition that spans cognitive domains. The MMSE⁶³, a brief screening tool, was used in inclusion criteria for the BECT and as a measure of global cognitive function. Due to the restricted range (24-30), we used a median split to create a dichotomous score; odds ratios indicated a lower vs higher MMSE score.

Executive Function

Executive function includes cognitive processes related to strategic organization and complex goal-oriented tasks. Tests of executive function included the Trail Making Test (TMT) and the Stroop test. The TMT consisted of two parts: TMT-A and TMT-B. TMT-A requires participants to draw a line connecting the numbers 1-25 sequentially, as fast as they can without picking their pencil up from the paper. The final score is the time to complete the task. TMT-B has similar task requirements to TMT-A, but requires participants to alternate between numbers and letters (e.g., 1-A-2-B...L-13). The TMT summary score was calculated by subtracting TMT-A from TMT-B⁸⁸. This test was only administered to the subset of participants within the BHS.

The Stroop task was measured using the automated cognitive frailty instrument developed by Carlson⁸⁹. This test required participants to register their responses to trials on a wireless keypad with “red,” “green,” and “blue” colored buttons. Reaction time in milliseconds was recorded for each trial. The Stroop test consisted of two conditions. Condition 1, the color naming task, required participants to name the color ink of a neutral stimulus (a series of X’s). Condition 2, the color word task, required participants to name the color ink of an incompatible word (e.g., the word RED in green ink). The total score, or Stroop effect, was calculated by subtracting the average reaction time for correctly answered trials of Condition 1 from Condition 2. This test was administered to all participants in the BECT.

Memory

Memory, the process by which information is encoded, stored, and retrieved, includes long-term declarative memory. Memory was measured using the Rey Auditory Verbal Learning Test (RAVLT)⁹⁰. Participants were presented with a 15-word list (List A) and asked to recall words for five learning trials. The total number of words recalled over the five trials was considered the learning score. After the fifth trial, the test administrator presented an interference list of 15 words not on the original list, and participants were instructed to repeat those new words. Next, without the administrator reading the original list, participants were instructed to name as many words from the original list as they could remember. After at least 15 minutes, the participant was again asked to recall words from the original list. The total number of words recalled correctly was considered the long-term memory score. This test was administered to all participants in the BECT.

Processing Speed

Processing speed is a basic cognitive process that is part of many other cognitive domains and is related to the amount of time required to process a set amount of information. Processing speed was assessed using the pattern comparison test⁹¹. Participants were required to decide whether two side-by-side patterns were the same or different within a fixed time frame (30 seconds). Participants completed two sets of trials of increasing difficulty; the total score was the number of correct responses on both trials. This test was administered to all participants in the BECT.

Hippocampal and Thalamus Volume

The hippocampus is a brain structure located in the medial temporal lobes and plays a key role in the consolidation of information essential to memory. Hippocampal atrophy is also associated with memory impairment and dementia ⁹²⁻⁹⁴ and may serve as a key biomarker in early and presymptomatic diagnosis of AD ^{95, 96}. The thalamus is a brain region used in prior physical activity studies as a control to explore hippocampal specific effects ⁹⁷. High resolution brain images were acquired on a 3.0T Phillips scanner (Best, the Netherlands) using a 3D T1-weighted MPRAGE sequence (Magnetization Prepared Rapid Gradient Echo Imaging) with the following parameters: repetition time (TR)= 8.037 ms; echo time (TE)= 3.7 ms; flip angle= 8°; 200 contiguous 1mm sagittal slices; FOV= 200 mm × 256 mm × 200 mm; matrix size=256mm × 256 mm; voxel size (1x1x1mm); protocol has been described previously ^{66, 98}. Segmentation of hippocampal volumes, were performed using FMRIB's Integrated Registration and Segmentation Tool (FIRST) in FMRIB's Software Library (FSL) version 4.1 ⁹⁹ and has been successfully used previously in older adult populations (e.g., ^{97, 100}) and validated against other automated methods and manual tracing ^{101, 102}. FIRST is a model-based segmentation/ registration tool using a Bayesian framework from shape and appearance models obtained from manually segmented images from the Center for Morphometric Analysis, Massachusetts General Hospital, Boston. Briefly, images were first registered to MNI (Montreal Neurological Institute) 152 standard space using 2-stage affine transformations based on 12-degrees of freedom. A subcortical mask was then applied to exclude voxels outside the subcortical regions. Then the volumes were segmented with 30 modes of variation. Last, boundary correction was performed to classify the boundary voxels as belonging to the structure or not according to a statistical probability (z score > 3.00; p<0.001). Additional pre-processing steps included motion correction and non-uniform intensity normalization. All processed images were then visually inspected to identify any significant errors resulting from the segmentation process. No participants were excluded due to segmentation errors.

All brain volumes (hippocampus, thalamus) were adjusted for sex and height using a measure of intracranial volume (ICV) as a covariate in all analyses. ICV was calculated as the sum of gray, white, and cerebrospinal fluid using FMRIB's automated segmentation tool in FSL version 4.1 ^{103, 104}, and used as a covariate in all analyses. Hippocampal volume was only collected from the subset of participants in the BHS. Of 123 participants enrolled in the BHS, 10 participants did not complete the MRI evaluation due to excessive head movement or claustrophobia, leaving a final sample of 113.

Covariates

In order to control for potential confounders of the relationship between physical activity and physical and cognitive function, all models included a number of covariates associated with both the dependent (physical function and cognitive function/ brain health) and explanatory variables (physical activity) in prior studies. These included age, sex, and race in the physical function models. The models examining the association between physical activity and cognitive function additionally included cardiovascular (CVD) burden, and education. The models examining the association between physical activity and brain structure additionally included ICV. CVD burden was calculated by summing participants' self-report of hypertension, diabetes, heart attack/ myocardial infarction, intermittent claudication, congestive heart failure, and angina/ chest pain due to heart disease.

Statistical Analyses

We first compared baseline socio-demographic and health characteristics of participants offered the SAMs and those in the BHS, with those in the larger BECT using chi-square tests for dichotomous variables and t-tests for continuous variables (Table 1). Next we explored the distributions of the predictors and continuous outcomes. All metrics of low-intensity physical activity measured by the SAM were approximately normally distributed. CHAMPS variables were log transformed due to their skewed distribution. We then compared the baseline physical activity characteristics between groups, including percentage meeting physical activity guidelines using both objective (SAM) and self-report (CHAMPS) measures. We additionally reported average low-intensity and moderate-intensity walking activity measured by the SAM and physical activity measured by the CHAMPS.

The primary objective of the analysis was to 1) examine the associations between the low-intensity SAM and CHAMPS physical activity metrics and physical function, cognitive function, and brain structure variables, and to examine the associations of low-intensity physical activity independent from moderate-intensity physical activity. Multiple linear and logistic regression using Stata version 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX:

StataCorp LP) were used to model the relationship between the binary and continuous dependent variables (physical function, cognitive function, and brain structure). The models described below were fit using the least squares approach to estimate model parameters. Standardized Beta (β) coefficients, standard errors (SE), and p-values of two-sided statistical tests are presented in Tables.

Model 1A (Table 3) explored the relationship between the SAM and CHAMPS metrics, and physical function; Model 1B explored the same relationship including moderate- to vigorous-intensity metrics as an additional covariate. Model 2A (Table 4) explored the relationship between the SAM and CHAMPS metrics, and cognitive function; Model 2B (Table 5) explored the same relationship including moderate- to vigorous-intensity metrics as an additional covariate. Model 3A (Table 6) explored the relationship between the SAM and CHAMPS metrics and brain volume, including the hippocampus and thalamus brain regions; Model 3B explored the same relationship including moderate- to vigorous-intensity metrics as an additional covariate.

Logistic regression models were used to analyze the two binary physical function measures; model results were expressed as a unit increase in physical activity metrics associated with an increased/decreased odds of reporting “Difficulty with one flight of steps,” and “Ability to balance.” Linear regression models were used to analyze the continuous physical and cognitive function measures; model results were expressed as a unit increase in physical activity metrics associated with an increase/decrease in the specific function measure. Estimated effect sizes for the CHAMPS metrics, caloric expenditure, were expressed in units of 100 calories/day. Estimated effect sizes for the SAM metrics, steps/day (amount), were expressed in units of 1000 steps/day based on previous studies as well as ease of interpretation¹⁰⁵. Regression diagnostics for outliers, normality of residuals, and checks for multicollinearity were performed by visual inspection of residual plots, and computation of variance inflation factors. Tobit regression and robust standard errors were used for all regression models where health measures had censoring or skew.

Analyses between physical activity metrics and cognitive and brain structure outcomes specifically were sex stratified a-priori given differences in the association between physical activity/ exercise and neurocognition^{57, 106, 107}; the BECT and BHS were additionally designed to allow for sex stratification in analyses⁶².

Results

Socio-demographic and physical activity characteristics

Table 1 presents baseline characteristics of the sample offered the SAMs (SAM sample) and the larger BECT sample. We describe these characteristics for the entire BECT sample only unless characteristics differed significantly ($P<.05$) between the SAM and BECT samples. Participants averaged 67.4 years, and were predominately female (90.5%) and African-American, with 42.6% reporting high school or less education, and 29.6% reporting household income less than \$15,000. Rates of chronic disease were high; 57.0% of participants were obese, 73.7% reported hypertension, 59.0% reported osteoarthritis, and 31.7% reported diabetes. Participants offered the SAMs varied significantly ($p<.05$) from those in the larger BECT by sex (76.5% female) and education (36.4% reporting high school or less education).

Table 2 presents baseline physical activity characteristics of the samples. According to the 150 minutes per week of moderate-intensity physical activity guideline, the CHAMPS self-report questionnaire indicated that 61.5% of participants were considered active. According to the 10,000 steps/day walking activity guideline, the SAM objective measure indicated that 7.0% of participants were considered active. According to Department of Health and Human Services guidelines of 30 minutes of moderate-intensity activity/day, the SAM objective measure additionally indicated that no participants met guidelines by completing three or more 10-minute bouts/day of 1000 steps/ bout. Participants expended 2066.1 (SD: 1526.0) calories/week in low-intensity physical activity, and 2106.4 (SD: 2438.6) calories/week in moderate- to vigorous-intensity physical activity. Participants offered the SAMs had significantly ($p<.05$) greater moderate- to vigorous intensity physical activity than those in the larger BECT: a larger percentage were active (67.9), and expended more calories/ week (2553.9 (SD: 2856.5)) of moderate- to vigorous-intensity physical activity. Considering SAM measures of physical activity, the majority of activity was in the low-intensity range (6888.1 (SD: 2835.9) steps/day) with minimal activity in the moderate- to vigorous-intensity ranges (760.7 (SD: 1121.6) steps/day).

Low-intensity physical activity and physical function

Table 3 presents the associations between low-intensity physical activity metrics and physical function measures after adjusting for age, sex, and race. In Model 1A where low-intensity activity was included as the only physical activity independent variable, SAM low-intensity walking activity was associated with physical function, and no CHAMPS low-intensity physical activity metrics were associated with physical function. An additional 1000 steps/day at low-intensity was significantly associated with a 16% reduction in the odds of reporting difficulty with one flight of steps (OR: 0.84. 95% CI: 0.72, 0.97); a .09 second faster usual walking speed (95% CI: -0.15, -0.04) and a 0.08 second faster rapid walking speed (95% CI: -0.12, -0.04); 0.22 seconds faster on the chair stands strength task (95% CI: -0.37, -0.07) and a 0.20-point increase in SPPB (95% CI: 0.10, 0.31). In Model 1B after adding moderate- to vigorous-intensity physical activity as an additional covariate, the majority of SAM low-intensity walking activity metrics remained significant; all moderate- to vigorous-intensity CHAMPS metrics were significantly associated with physical function, and, as expected, CHAMPS low-intensity physical activity metrics continued to not have a significant association with physical function. An additional 1000 steps/day at low-intensity was significantly associated a .08 second faster usual walking speed (95% CI: -0.15, -0.02) and a 0.07 second faster rapid walking speed (95% CI: -0.12, -0.02); and a 0.16-point increase in SPPB (95% CI: 0.05, 0.28). An additional 1000 calories of moderate- to vigorous-intensity physical activity measured by the CHAMPS was associated with a 9% reduction in the odds of reporting difficulty with one flight of steps (OR: 0.91. 95% CI: 0.85, 0.97); a .11 second faster usual walking speed (95% CI: -0.14, -0.07) and a 0.06 second faster rapid walking speed (95% CI: -0.08, -0.03); 0.16 seconds faster on the chair stands strength task (95% CI: -0.24, -0.07) and a 0.17-point increase in SPPB (95% CI: 0.10, 0.23).

Low-intensity physical activity and cognition function

Table 4 and Table 5 present the sex-stratified associations between low-intensity physical activity metrics and cognitive function measures after adjusting for age, race, education, and CVD burden. Across all cognitive function measures, including global cognition, executive function, RAVLT, and pattern comparison, in Model 2A (Table 4) where low-intensity activity was included as the only physical activity independent variable, SAM low-intensity walking activity was associated with memory in only women, and CHAMPS low-intensity physical activity was not associated with cognitive function in men or women. An additional 1000 steps/day at low-intensity was

significantly associated with 0.59 more words remembered in the learning memory score (95% CI: 0.15, 1.04), and 0.19 more words recalled in the long-term memory score (95% CI: 0.02, 0.35). In Model 2b (Table 5) after adding moderate- to vigorous intensity physical activity as an additional covariate, SAM low-intensity walking activity remained associated with memory in women; as expected CHAMPS low-intensity physical activity metrics continued to have no significant association with cognitive function in men or women. An additional 1000 steps/day at low-intensity was significantly associated with 0.56 more words remembered in the learning memory score (95% CI: 0.07, 1.05), and 0.20 more words recalled in the long-term memory score (95% CI: 0.03, 0.38). There was no significant association in men.

Low-intensity physical activity and hippocampal volume

Table 6 presents the sex-stratified associations between low-intensity physical activity metrics and brain structure measures after adjusting for age, race, education, CVD burden, and ICV. In Model 3A, where low-intensity activity was included as the only physical activity independent variable, SAM low-intensity walking activity was associated with hippocampal volume in women and CHAMPS low-intensity physical activity was not associated with hippocampal volume in men or women. An additional 1000 steps/day at low-intensity was significantly associated with a 0.09 cm³ larger hippocampal volume (95% CI: 0.01, 0.15). In Model 3B, after adding moderate- to vigorous intensity physical activity as an additional covariate, SAM low-intensity walking activity remained associated with hippocampal volume in women; as expected CHAMPS low-intensity physical activity continued to have no significant association with cognitive function in men or women. An additional 1000 steps/day at low-intensity was significantly associated with a 0.08 cm³ larger hippocampal volume (95% CI: 0.01, 0.15). There was no significant association with hippocampal volume in men. Across both models, low-intensity physical activity was not associated with thalamus volume in women or men.

Discussion

In a community-based cohort of urban-dwelling, older adults, we observed a wide discrepancy in the percent that met physical activity guidelines, with only seven percent meeting guidelines using an objective measure of walking activity, and almost 61.5% meeting guidelines using a self-report

measure of physical activity. In cross-section, greater low-intensity walking activity measured by the SAM was associated with a range of physical function measures, and these associations remained significant for walking, leg strength, and lower extremity strength outcomes when including moderate-intensity walking activity as a covariate. Low-intensity self-report physical activity measured by the CHAMPS was not associated with better physical function, cognitive function, or brain structure. However, moderate-intensity physical activity was independently associated with all physical function measures. In cross-section, greater low-intensity walking activity measured by the SAM was associated with memory in women according to both behavioral scores (RAVLT) as well as hippocampal volume, and both relationships remained significant independent of moderate-intensity walking activity.

Overall this study's findings provide evidence for the physical and cognitive function benefits of low-intensity walking activity, a range of activity that is much more common than moderate-intensity activity and may serve as an achievable target to maintain and promote health. Results additionally indicate that objective physical activity devices are extremely important to accurately capturing physical activity within the low-intensity range.

Physical activity characteristics

The SAM and the CHAMPS determined physical activity guidelines varied considerably in their estimation of the percentage of individuals considered active. The discrepancy in objective and self-report measures in assessments of physical activity broadly, as well as in assessments of adherence to physical activity guidelines, is expected^{108, 109}. Similar to this study's findings, self-report metrics generally estimate a greater percentage of adherence compared to objective metrics¹⁰⁹. Again, similar to other studies, these discrepancies need to also be considered within the context of varying methodologies to calculate adherence^{44, 110} as well as the differences in walking activity compared to physical activity (this is expanded in the limitations section below). While physical and walking activity measures chosen in this study may not be the most appropriate to measure adherence to physical activity guidelines, we can conclude that the objective measures indicate that participants were generally non active, largely sedentary, and therefore at-risk for negative health outcomes related to lower walking activity levels. It is important to additionally note that the SAM sample and the BECT sample were similar in the

majority of demographic and health characteristics; the SAM sample was however slightly more physically active due to a greater moderate- to vigorous-intensity physical activity/week.

Physical activity and physical function

The SAM was designed to precisely measure walking activity in older adult populations with varying levels of function^{69, 70}, and can differentiate between walking activity intensity. In this study, low-intensity walking activity measured by the SAM was significantly associated with performance-based measures of walking (usual and rapid gait speed) and overall lower-extremity function, including strength, walking, and balance components, independent of the relationship between moderate-intensity walking activity and physical function outcomes. Physical function decline is a characteristic of aging and is part of the decline that may precede physical disability characterized by functional limitations^{111, 112}. While cross-sectional, this relationship indicates that perhaps walking activity at low-intensity, which may include non-exercise leisure-time activities and instrumental activities of daily living, as well as low-intensity exercise, may serve as a target in future designs of achievable and sustainable activity interventions in otherwise sedentary individuals.

Low-intensity physical activity measured by the CHAMPS, which includes walking leisurely, light gardening, and housework, was not associated with any physical function outcome. These low-intensity activities are often very difficult to reliably measure with self-report measures^{44, 45}. CHAMPS measures of moderate- to vigorous intensity physical activity, however, which included aerobic and strength training exercises, were associated with all physical function measures. This relationship was expected considering activity guidelines based on the physical function and health benefits of exercise and other moderate-intensity physical activity.

Physical Activity, Cognitive Function and Brain Structure

Low-intensity walking activity measured by the SAM was significantly associated with both functional/ behavioral and brain structural measures of memory in women. A number of studies have found that physical exercise and greater levels of physical activity are associated with verbal memory (e.g.,^{113, 114}). Recent neurobiological evidence additionally indicates that exercise

training may reduce brain atrophy in non-demented individuals ¹¹⁵⁻¹¹⁷, and exercise and fitness may have a positive effect specifically on the size of the hippocampus ^{97, 100, 115}. This study provides strong evidence for the cross-sectional association between low-intensity walking activity and memory, and underscores the importance of exploring whether modest increases in non-exercise, lifestyle activities in the low-intensity range may promote cognitive health related to memory and reduced risk of dementia.

CHAMPS measures of physical activity were not associated with cognitive function or brain structure. This lack of an association may be partially driven by measurement; the SAM and other objective measures of physical and walking activity may be important to accurately measure walking activity within a community setting, particularly among mostly sedentary older adults at elevated risk for cognitive and functional decline. Recent research utilizing objective physical activity monitors that can sensitively measure a broad range of physical activities in-community, suggest that non-exercise physical activity may also be associated with cognitive health benefits ^{12, 118}. The results from this study expand this body of evidence to suggest that non-exercise walking activity within the low-intensity range may be associated with the same brain region most consistently shown to be affected by increased aerobic fitness and exercise. These findings encourage us to better understand whether increasing non-exercise, lifestyle physical activities may produce measurable cognitive benefits and affect hippocampal volume through molecular pathways unique to those related to moderate-intensity exercise ¹¹⁹.

Limitations

This study has limitations. First the study was cross-sectional in design; this precludes causal inferences. Second, while we were exploring associations between physical activity and cognitive and physical function, comparing self-report and objective measures, it is very important to note that the CHAMPS measured kilocalories expended in physical activity while the SAM measured walking activity. These measures vary not only in the modality of measurement, but also in what is being measured and therefore comparisons between both need interpreted carefully. Third, the SAM was placed on the ankle versus the hip. While this placement allows the SAM to detect steps in participants with altered gait, we did not capture non-ambulatory movement associated with trunk and upper body activities, a component of total daily physical activity. Fourth, for those

with very low levels of activity, exclusion criteria removing days with less than six hours of activity may have resulted in an underestimation of individuals who were very sedentary. However, the effect of any bias was likely minimal given the extremely low overall rates of moderate to vigorous-intensity activity. Finally, while the study sample represented an understudied and at-risk segment of the older adult population, a trial of high-intensity volunteer service may select for the more health conscious and physically active members of the community^{120, 121}. Therefore, study results may represent a conservative estimate of walking activity and health relative to the larger older adult population.

Conclusions

Objectively measuring daily walking activity in a largely sedentary and at-risk older adult population demonstrated the importance of low-intensity levels of walking activity to numerous health measures, including physical and cognitive function, and brain health. These positive associations highlight the need to better characterize and understand how increasing daily levels of low-intensity walking in various ways may be associated with the prevention of physical and cognitive disability in the aging population.

Table 1. Baseline demographic and health characteristics of study participants

	SAM sample n = 187	BECT sample n = 702
Characteristic	N (%) or Mean \pm SD	N (%) or Mean \pm SD
Age (years)	66.8 \pm 5.6	67.4 \pm 5.9
Female	143 (76.5)*	596 (84.9)
Race (African American)	169 (90.4)	635 (90.5)
Education (\leq high school)	68 (36.4)*	299 (42.6)
Income (< \$15,000)	52 (28.0)	204 (29.6)
Chronic Disease		
Obesity (BMI \geq 30)	109 (58.3)	400 (57.0)
Hypertension	131 (71.2)	495 (73.7)
Osteoarthritis	113 (61.8)	397 (59.0)
Diabetes	60 (32.6)	213 (31.7)
Health and functioning		
Difficulty with 1 flight of stairs	44 (23.5)	178 (25.5)
Lower extremity function (SPPB) ^a	9.1 \pm 2.1*	8.4 \pm 2.2
Global Cognition (MMSE) ^b	28.3 \pm 1.52	28.1 \pm 1.56

Note. SD = standard deviation; SAM = step activity monitor; BECT = Baltimore Experience Corps Trial; SPPB = Short Physical Performance Battery; MMSE = Mini-Mental State Exam

* $p < .05$ for chi-square or t-test analyses comparing SAM sample to BECT sample (excluding the SAM sample)

Table 2. Baseline physical activity characteristics of study participants

	SAM sample n = 187	BECT sample n = 702
Characteristic	N (%) or Mean \pm SD	N (%) or Mean \pm SD
% meeting physical activity guidelines		
CHAMPS		
150 minute/ week of moderate-intensity physical activity ^a		
Active (≥ 150 minutes/week)	127 (67.9)*	431 (61.5)
SAM		
10,000 steps/day ^b		
Active ($\geq 10,000$ steps/day)	13 (7.0)	-
30 minutes of moderate intensity activity ^c		
Active (≥ 30 minutes/day)	2 (1.1)	-
Activity Metrics		
CHAMPS		
Caloric expenditure/week: Low-intensity ^d	2010.8 \pm 1459.7	2066.1 \pm 1526.0
Moderate- to vigorous-intensity ^d	2553.9 \pm 2856.5*	2106.4 \pm 2438.6
SAM		
Steps/day: Low-intensity ^e	6888.1 \pm 2835.9	-
Moderate- to vigorous-intensity ^e	760.7 \pm 1121.6	-

SAM = step activity monitor; BECT = Baltimore Experience Corps Trial; CHAMPS = Community Health Activities Model Program for Seniors

^a 150 minute/week of moderate-intensity physical activity considered the U.S. physical activity guideline

^b 10,000 steps/day considered an estimate of daily recommended walking activity

^c 30 minutes/day of moderate intensity activity (≥ 100 steps/min) considered an estimate of daily recommended walking activity

^d low-intensity activity measured by CHAMPS includes activities with metabolic equivalent (MET) values < 3.0; moderate- to vigorous-intensity activity measured by the CHAMPS includes activities with MET values ≥ 3.0 .

^e low-intensity activity measured by the SAM is defined as walking activity at < 100 steps/min; moderate- to vigorous-intensity activity measured by the SAM is defined as activity at ≥ 100 steps/min

* $p < .05$ for chi-square or t-test analyses comparing SAM sample to BECT sample (excluding the SAM sample)

Table 3. Associations between metrics of low-intensity physical activity and physical function

		MODEL 1A							
		Mobility		Walking				Leg strength	
		Difficulty with stairs		Normal		Rapid		Chair stands	
								Lower extremity function	
		OR	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)
SAM metrics									
Low-intensity walking activity (steps/day)		0.84*	(0.72, 0.97)	-0.09**	(-0.15, -0.04)	-0.08**	(-0.12, -0.04)	-0.22**	(-0.37, -0.07)
CHAMPS metrics									
Low-intensity physical activity (calories /week)		0.89	(0.73, 1.08)	-0.01	(-0.13, 0.10)	0.01	(-0.07, 0.08)	-0.23	(-0.49, 0.03)
								0.03	(-0.17, 0.22)
		MODEL 1B							
		Mobility		Walking				Leg strength	
		Difficulty with stairs		Normal		Rapid		Chair stands	
								Lower extremity function	
		OR	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)
SAM metrics									
Low-intensity walking activity (steps/day)		0.87	(0.74, 1.01)	-0.08*	(-0.15, -0.02)	-0.07**	(-0.12, -0.02)	-0.16	(-0.32, 0.01)
Moderate- to vigorous intensity walking activity (steps/day)		0.77	(0.49, 1.20)	-0.08	(-0.24, 0.08)	-0.06	(-0.17, 0.05)	-0.38	(-0.78, 0.04)
CHAMPS metrics									
Low-intensity physical activity (calories /week)		0.94	(0.77, 1.15)	0.05	(-0.06, 0.17)	0.04	(-0.03, 0.12)	-0.14	(-0.41, 0.12)
Moderate- to vigorous intensity physical activity (calories/week)		0.91**	(0.85, 0.97)	-0.11**	(-0.14, -0.07)	-0.06**	(-0.08, -0.03)	-0.16**	(-0.24, -0.07)
								0.17**	(0.10, 0.23)

* p<.05 ; ** p<.01

Table 4. Associations between metrics of low-intensity physical activity and cognitive function (part1)

MODEL 2A												
Global Cognition MMSE					Executive Function Trails				Executive Function Stroop			
Men		Women			Men		Women		Men		Women	
	OR	(95% CI)	OR	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)
SAM metrics												
Low-intensity walking activity (steps/day)	0.84	(0.65, 1.10)	1.00	(0.88, 1.13)	0.16	(-0.03, 0.35)	-0.08	(-0.18, 0.01)	0.00	(-0.04, 0.05)	0.01	(-0.02, 0.04)
CHAMPS metrics												
Low-intensity physical activity (calories /week)	0.78	(0.48, 1.28)	0.95	(0.76, 1.19)	-0.18	(-0.93, 0.56)	0.01	(-0.31, 0.32)	0.05	(-0.12, 0.22)	0.00	(-0.07, 0.07)
MODEL 2A (continued)												
Learning RAVLT					Long-term memory RAVLT				Processing Speed Pattern Comparison			
Men		Women			Men		Women		Men		Women	
	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)
SAM metrics												
Low-intensity walking activity (steps/day)	-0.40	(-1.23, 0.45)	0.59*	(0.15, 1.04)	-0.28	(-0.64, 0.08)	0.19*	(0.02, 0.35)	-0.03	(-0.59, 0.53)	0.23	(-0.07, 0.53)
CHAMPS metrics												
Low-intensity physical activity (calories /week)	0.11	(-1.34, 1.57)	0.06	(-0.90, 0.92)	0.45	(-0.14, 1.04)	0.07	(-0.27, 0.40)	0.19	(-0.79, 1.17)	-0.38	(-1.01, 0.24)

* p<.05 ; ** p<.01

Table 5. Associations between metrics of low-intensity physical activity and cognitive function (part 2)

	MODEL 2B											
	Global Cognition MMSE				Executive Function Trails				Executive Function Stroop			
	Men		Women		Men		Women		Men		Women	
	OR	(95% CI)	OR	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)
SAM metrics												
Low-intensity walking activity (steps/day)	0.77	(0.56, 1.04)	0.99	(0.86, 1.13)	0.03	(-0.25, 0.30)	-0.06	(-0.16, 0.05)	0.01	(-0.08, 0.06)	0.02	(-0.02, 0.05)
Moderate- to vigorous intensity walking activity (steps/day)	1.44	(0.65, 1.10)	1.06	(0.82, 2.51)	0.45	(-0.23,1.13)	-0.26	(-0.59, 0.07)	0.04	(-0.12, 0.21)	0.02	(-0.12, 0.07)
CHAMPS metrics												
Low-intensity physical activity (calories /week)	0.79	(0.48, 1.30)	0.98	(0.78, 1.24)	-0.22	(-0.97, 0.54)	0.03	(-0.30, 0.36)	0.06	(-0.11, 0.24)	0.00	(-0.07, 0.08)
Moderate- to vigorous intensity physical activity (calories/week)	0.98	(0.83, 1.16)	0.96	(0.90, 1.02)	0.09	(-0.13, 0.31)	-0.03	(-0.14, 0.08)	-0.03	(-0.09, 0.03)	0.00	(-0.03, 0.02)
MODEL 2B (continued)												
	Learning memory RAVLT				Long-term memory RAVLT				Processing Speed Pattern Comparison			
	Men		Women		Men		Women		Men		Women	
	β	(95% CI)	B	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)
SAM metrics												
Low-intensity walking activity (steps/day)	-0.14	(-1.09, 0.81)	0.56*	(0.07, 1.05)	-0.26	(-0.68, 0.15)	0.20*	(0.03, 0.38)	0.05	(-0.59, 0.70)	0.24	(-0.09, 0.57)
Moderate- to vigorous intensity walking activity (steps/day)	-1.00	(-2.78, 0.77)	0.27	(-1.27, 1.81)	-0.06	(-0.84, 0.72)	-0.13	(-0.70, 0.44)	-0.32	(-1.52, 0.89)	-0.07	(-1.11, 0.97)
CHAMPS metrics												
Low-intensity physical activity (calories /week)	0.15	(-1.38, 1.69)	0.04	(-0.84, 0.92)	0.41	(-0.22, 1.03)	0.06	(-0.28, 0.40)	-0.08	(-1.10, 0.94)	-0.45	(-1.10, 0.19)

Moderate- to vigorous
intensity physical activity
(calories/week)

-0.05	(-0.66, 0.56)	0.03	(-0.22, 0.28)	0.06	(-0.19, 0.31)	0.01	(-0.08, 0.10)	0.35	(-0.07, 0.76)	0.09	(-0.10, 0.27)
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* p<.05 ; ** p<.01

Table 6. Associations between metrics of low-intensity physical activity and hippocampal volume

Model 3A								
Hippocampus (cm3)					Thalamus (cm3)			
Men		Women			Men		Women	
	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)
SAM metrics								
Low-intensity walking activity (steps/day)	0.00	(-0.01, 0.11)	0.09*	(0.01, 0.15)	-0.06	(-0.22, 0.09)	-0.01	(-0.10, 0.07)
CHAMPS metrics								
Low-intensity physical activity (calories /week)	0.25	(-0.23, 0.73)	0.17	(-0.01, 0.35)	0.29	(-0.32, 0.90)	0.03	(-0.29, 0.26)
Model 3B								
Hippocampus (cm3)					Thalamus (cm3)			
Men		Women			Men		Women	
	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)
SAM metrics								
Low-intensity walking activity (steps/day)	-0.05	(-0.22, 0.12)	0.08*	(0.01, 0.15)	-0.08	(-0.30, 0.14)	0.01	(-0.01, 0.10)
Moderate- to vigorous intensity walking activity (steps/day)	0.17	(-0.24, 0.57)	0.06	(-0.15, 0.27)	0.06	(-0.47, 0.60)	-0.22	(-0.50, 0.05)
CHAMPS metrics								
Low-intensity physical activity (calories /week)	0.25	(-0.24, 0.73)	0.12	(-0.06, 0.31)	0.30	(-0.32, 0.92)	0.04	(-0.20, 0.28)
Moderate- to vigorous intensity physical activity (calories/week)	0.00	(-0.14, 0.14)	0.06	(0.00, 0.13)	-0.04	(-0.22, 0.14)	-0.01	(-0.09, 0.07)

* $p < .05$; ** $p < .01$

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Chapter 6.

Aim 2: Effect of Experience Corps on physical activity:
randomized clinical trial results

Introduction

Physical inactivity is associated with higher risk of adverse health outcomes including all-cause mortality ^{1,2}, falls and fractures ³, metabolic syndrome ⁴, diabetes ^{5,6}, functional limitations ⁷, and cognitive decline ^{8,9} and dementia¹⁰⁻¹². Greater amounts of daily physical activity can help prevent chronic illness and decline. However, only 20% of older adults meet the aerobic and muscle strengthening components of U.S. physical activity guidelines ¹³⁻¹⁵. Although evidence from randomized control trials has shown that exercise interventions in older adults are effective at increasing physical activity ^{16, 17}, many older adults have difficulty initiating and adhering to exercise programs ^{18, 19}, and cross-sectional evidence using both self-report and objective measures indicates that physical activity and fitness declines with age ²⁰⁻²⁴. These consistent epidemiological findings are of particular concern for minority older adults as well as those of low socio-economic status (SES) who, compared to non-minority and high SES individuals, have lower baseline levels of physical activity, greater chronic disease burden, and access to fewer physical activity-related facilities due to restrictive environment and neighborhood characteristics ^{15, 25-28}.

Physical activity interventions targeting older adults can include exercise interventions where individuals are given specific exercise prescriptions, including walking, stretching, and strength training ¹⁶. Alternatively, lifestyle physical activity interventions, which include those targeting non-exercise physical activities (e.g., leisure time activities and household activities), are typically tailored to specific populations and generally involve short bouts of activity accumulated throughout the day ^{29, 30}. These interventions have been shown to be effective at increasing physical activity and may be viable alternatives to exercise interventions ³⁰⁻³². Traditional interventions explicitly target increasing physical activity, and the communication channels used to reach older adults and, particularly for group-based exercise interventions, the settings where those programs take place are also centered around those physical activities ^{16, 33, 34}.

Experience Corps (EC) represents a novel approach to physical activity interventions. Experience Corps is a community-based model of health promotion embedded within a volunteer service program. Experience Corps places older adults as volunteers within the public school system to simultaneously increase their physical, cognitive, and social activity, while improving the academic outcomes of children ^{35, 36}. Experience Corps Baltimore, established through a

partnership between the Johns Hopkins Center on Aging and Health and the Greater Homewood Community Corporation (GHCC), recruited older adults based on their desire to be generative, or “give back” rather than their desire to improve their health or increase their physical activity³⁷. The program was designed specifically to attract a diverse population of older adults who may not engage in typical exercise, lifestyle, and other health promotion interventions^{35, 37}.

Prior pilot results suggest that participating in EC may lead to short-term increases in self-reported physical activity that may continue outside the program^{35, 38, 39}, in addition to benefits to cognitive function^{40, 41} and increases in social activity³⁵. These promising results led to the development of a large-scale, randomized controlled trial (RCT) titled the Baltimore Experience Corps Trial (BECT)⁴² and its nested objective physical activity and neuroimaging sub study, the Brain Health Study (BHS)⁴³. Here we report on the effectiveness of the long-term, two-year intervention to increase physical activity in an older, mostly sedentary, cognitively intact cohort at elevated risk for cognitive and functional decline. We specifically explored whether participants in the larger BECT randomized to the EC intervention, compared to controls, showed increased self-report physical activity. Within the BHS sub-study, we additionally explored whether intervention participants, compared to controls, showed increased objectively-measured walking activity.

Methods

Participants

Participants were from the BECT, a sex-stratified, randomized controlled effectiveness trial to evaluate the health benefits for older adults participating in EC Baltimore vs. a control group offered other low-service volunteer opportunities, and the BHS, a nested physical activity and neuroimaging trial within the BECT. Details on sex-stratified randomization, study design, sampling methodology, and recruitment are described elsewhere^{35, 42}. BECT enrollment criteria included 1) aged ≥ 60 years; 2) English speaking; 3) ≥ 24 on the Mini-Mental State Exam (MMSE)⁴⁴; and 4) ability to read at a minimum 6th grade level measured by the Wide Range Achievement Test⁴⁵. Participants consenting to the BECT were simultaneously offered the opportunity to participate in the BHS. BHS study design and enrollment criteria are described elsewhere^{43, 46},

and additionally included: 1) right-hand dominance; 2) free of a pacemaker or other ferrous metals in the body; and 3) no history of brain cancer or brain aneurism/stroke in the past year.

From 2006 to 2009, 702 participants were randomized to either the EC intervention (n=352) or the low-activity control (n=350). Of those, 123 were also simultaneously enrolled in the BHS (intervention: n = 59; control = 55). The CONSORT figure included in Figure 1 and Figure 2 summarizes the flow of participants through the BECT and BHS respectively, including dropout at baseline, 12-month, and 24-month follow-up evaluations. By design, the BHS over-sampled for men, and did not differ significantly ($p \leq 0.05$) from the remaining BECT participants on any socio-demographic or health characteristic at baseline other than sex. The study protocol was approved by the Johns Hopkins School of Medicine Institutional Review Board, and each participant provided written informed consent.

Experience Corps Intervention and BECT and BHS study designs

The EC intervention has been described in detail previously^{35,42}. The essential program elements of EC were developed to increase participation and appeal to older adults^{33,34}, reduce barriers to participate particularly for ethnic minorities and those of low SES⁴⁷, and were based on recommendations for promoting physical activity^{48, 49}. These elements included: 1) core, intergenerational, generative, and high-impact volunteer roles; 2) a minimum of 15 hours/week of service during the academic year; 3) a critical mass of volunteers in each school and a team approach to provide social support and reinforcement; 4) training and infrastructure to support effectiveness and retention; 5) reimbursement for expenses; and 6) program flexibility and a diversity of roles to meet the needs and skills of individual volunteers³⁵.

Participants randomized to the EC intervention group attended a five-day, 30-hour standardized training program, including lecture discussion, exercise, role plays and handouts designed to provide volunteers with the necessary skills to volunteer in schools. Participants were then placed in Baltimore city public elementary schools in teams of 7-15 and served at least 15 hours/week for the full academic year. Experience Corps Baltimore volunteer roles, which were modified to be appropriate for individual volunteers and fit specific school needs, included literacy support,

math support, library support, behavior management and violence prevention activities, school attendance support, and computing support.

The BECT was designed in part to measure the effect of the two-year EC intervention on physical activity. Participants randomized to the intervention agreed to follow the intervention protocol described above and volunteer in the schools for two years (24 months), in addition to attending study evaluations at baseline (prior to the intervention) and at 8, 12, 14, 20, and 24 months ⁴². Self-report physical activity data were collected annually at baseline, 12 and 24 months. The study evaluation schedule was identical for control participants. The self-report physical activity measures used at annual visits were designed to capture physical activities that older adults within this study population were likely to complete; while the activities did not explicitly separate between within intervention and outside of intervention activities, the majority of activities were unrelated to the intervention (see detailed description below).

The BHS was designed in part to measure the effect of the EC intervention on levels and patterns of objectively measured walking activity outside the intervention. This was in response to evidence suggesting that physical activity often declines after interventions cease ⁵⁰ and recommendations to measure and better understand how interventions may impact the maintenance of physical activity ⁴⁷. By design, the majority of participants were evaluated in the summer and early fall (prior to the academic year) in order to capture daily walking activity outside the intervention and reduce seasonal bias. A detailed description of study protocol, including the explicit exclusion of intervention related walking activity, is included below.

Self-report physical activity measure

Physical activity was measured in all BECT participants using the Community Health Activities Model Program for Seniors (CHAMPS) questionnaire. The CHAMPS was developed in order to more sensitively measure variability among mostly underactive older adults by focusing on activities in the low-intensity range that may not be detected by commonly used questionnaires (e.g., Minnesota Leisure Time Physical Activity Questionnaire (MLTA)) that focus more on moderate- to vigorous-intensity physical activities. Several conceptual and methodological issues were considered when developing the CHAMPS, including 1) appropriate assessment of type,

amount, and frequency of physical activities; 2) designing questions and methods that will facilitate accurate measurement; 3) minimizing socially desirable response' and 4) enhancing sensitivity to change ⁵¹. The CHAMPS questionnaire used in the BECT was modified to fit within the study evaluation time, and include activities most common among the older adult population included in the study.

The CHAMPS was administered in-person to all BECT participants at baseline, 12, and 24 months by a trained evaluator. Participants were asked whether they participated in a range of physical activities in the past four weeks; for activities that participants engaged in, frequency of participation (times/week) and total hours (hours/ week) were assessed. The CHAMPS questionnaire assigns older adult specific metabolic equivalent (MET) values, or the energy cost, to each physical activity. The questionnaire therefore is able to distinguish activities by intensity. Low-intensity physical activities assessed by the CHAMPS include light housework around the house, and vigorous-intensity physical activity include jogging and running for exercise.

The CHAMPS questionnaire allows researchers to calculate caloric expenditure/week of physical activities. Using the American College of Sports Medicine formula (Table A1 of ⁵¹), caloric expenditure was calculated by multiplying hours/week of each activity by the corresponding MET value, by 3.5, and by body weight in kg/200. In addition to total caloric expenditure/week for all activities, we calculated total caloric expenditure/week for low-intensity physical activities, defined as all activities assigned <3.0 METs, and total caloric expenditure/week for moderate- to vigorous activities, including all activities assigned ≥ 3.0 METs.

Participants with missing data for >20% of the activities within the three metrics calculated from the CHAMPS questionnaire were excluded.

Objective walking activity measure

Objectively measured walking activity was measured using a Step Activity Monitor (SAM; Modus Health LLC, Washington, DC). The SAM is an accelerometer that is worn on the dominant ankle and measures step activity in daily life over continuous periods of time. The device measures the number of steps at one-minute intervals using acceleration, position, and timing information and

has been validated across a range of community-dwelling older adult populations with varying levels of function using self-report and objective measures (e.g., hand-tallied step counts and other accelerometers) ⁵²⁻⁵⁴. The SAM is particularly sensitive in measuring activity at decreased gait speeds ⁵³, and is well tolerated by older adults because it is placed on the ankle instead of the hip ⁵⁵.

The SAM was used to measure walking activity in all sub-study participants in the BHS at baseline, 12 and 24 months. At each BHS visit, evaluators blinded to intervention assignment calibrated the SAM by comparing hand-tallied step counts to one minute of walking activity at the participant's normal gait. Participants were instructed to wear the SAM for up to seven days while keeping a wear time/activity diary at approximately one-hour intervals. Participants were instructed to remove the SAM only when bathing, showering, or swimming, and replace the device immediately after. The data cleaning protocol included exclusion of days that represented noncompliance based on 1) objectively measured inactivity: a) less than 200 steps/day; days with less than a total of six hours of any walking activity between wake and sleep time; b) days with six consecutive hours of inactivity (<1 step) between wake and sleep times ⁵⁶; and 2) participants' self-report of not following data collection protocol in activity diaries. Detailed cleaning protocol has been described previously ⁵⁷.

The SAM allows for the estimation of walking intensity (effort associated with walking). Intensity ranges included low-intensity (> 0 steps/min and < 100 steps/min) and moderate- to vigorous-intensity (\geq 100 steps/min) based on studies translating laboratory measurements of oxygen consumption while walking into pedometer-based metrics ^{58, 59}. Walking activity measures included total walking activity in steps/day as well as steps/day at low-intensity and steps/day at moderate- to vigorous intensity. All metrics were averaged across all valid days surveyed.

In order to characterize the proportion of participants meeting physical activity guidelines, we used the 10,000 steps/day threshold developed in previous studies as a reasonable equivalent of U.S. physical activity guidelines ^{60, 61} (Table 1). We classified participants who met the 10,000 steps/day threshold across all days surveyed as active. Based on previous studies translating physical activity recommendations (30 minutes of moderate-intensity activity/day that can be split into three, 10 minute bouts) into a pedometer based step goal (3 bouts/day of 1,000 steps

in 10 min^{58, 59}), we additionally classified participants who met the 3 bouts/day threshold across all days surveyed as active.

Statistical Analysis

The main objective of this study was to evaluate the effect of the EC intervention vs. control on total, low- and moderate- to vigorous-intensity physical activity, including self-report physical activity measured by the CHAMPS and walking activity measured by the SAM. All analyses were performed considering initial treatment assignment, rather than treatment compliance, to evaluate the effect of the intervention, and individuals who did not contribute study outcomes were excluded (CONSORT diagram Figure 1 & Figure 2).

We independently evaluated the effect of the EC intervention versus control on self-report physical activity and walking activity at 12 and 24 months. We log-transformed total and low-intensity caloric expenditure/week because of its skewed distribution. For these linear-log models, we expressed coefficients as a percentage change for ease of interpretation. Moderate- to vigorous-intensity caloric expenditure was expressed in kilocalories (scaled by 1000) to ensure for model convergence. Moderate- to vigorous-intensity walking activity was also scaled by 1000 to ensure for model convergence. Mixed effect models (i.e., multi-level models) to account for subject-level clustering were used to model total and low-intensity caloric expenditure/week as well as total and low-intensity walking activity. For moderate- to vigorous-intensity caloric expenditure/week and walking activity, because of over-dispersion of the data as well as a large number of 0 values (individuals who did not complete any moderate-intensity physical activity), we modeled the negative-binomial distributed data using negative binomial longitudinal regression.

All models included the following terms: CHAMPS (caloric expenditure/week) or SAM (steps/week physical activity variable or objective measured daily walking activity, visit (baseline, 12 month, 24 month), intervention status, intervention by visit interaction terms, and covariate age at baseline. Based on significant differences between baseline characteristics of BECT study participants by randomization, we additionally adjusted sex-stratified CHAMPS models for education and hypertension in men. Based on significant differences between baseline

characteristics of BHS study participants by randomization, we additionally adjusted sex-stratified walking activity models for BMI in women. Visit and intervention status were modeled as categorical variables with the baseline visit equal to time zero and the control group as the reference category. Based on exploration of autocorrelation of residuals by visit and determining optimal model fit using Akaike information criteria (AIC), the covariance matrix was modeled using an exchangeable structure. Beta coefficient estimates were calculated using least square means. We estimated the following at 12 and 24 months: 1) intervention effect: intervention minus control group; and 2) change in physical activity compared to baseline for the intervention and control group.

All statistical tests were two-sided and performed using Stata version 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

Results

Participants

From 2006-2009, 702 participants were randomized to the BECT and 123 participants were randomized to the BHS substudy. In the BECT, 352 were allocated to the EC intervention, and 350 were allocated to the control group; within the BHS, 65 were allocated to the intervention, and 58 were allocated to the control (CONSORT Figure 1 and Figure 2). Participants who agreed to participate in the BHS were randomized independently of the BECT. In the BECT, 3 participants (2 intervention, 1 control) did not provide any usable CHAMPS data and were excluded, and 699 participants (350 intervention, 349 control) were included in all analyses. In the BHS, 9 participants (6 intervention, 3 control) did not provide usable SAM data and were excluded, and 114 participants (59 intervention, 55 control) were included in all analyses.

Table 1 and Table 2 present baseline characteristics of the study samples. In the overall trial (BECT), a large percentage of participants had low education (43.4% reporting high school or less education) and low income (29.2% reporting household income less than \$15,000). Participants were additionally at risk for cognitive and physical function decline due to high rates of chronic disease: 56.9% of participants were obese (BMI \geq 30), 73.8% reported hypertension, and 31.7%

reported diabetes. BECT and BHS participants did not differ on any socio-demographic characteristic at baseline other than sex. Considering differences by sex, in the BECT sample, women had significantly greater BMI ($p<0.01$), lower income ($p<0.05$), lower education ($p<0.01$), and a larger percentage were African American ($p<0.05$), compared to men. Considering differences by randomization, in the total sample for the BECT and the BHS, intervention and control groups did not differ significantly on any measure other than exposure; in the sex-stratified BECT sample, intervention and control groups differed significantly by age, education, and hypertension in men. In the sex-stratified BHS sample, intervention and control groups differed significantly by BMI in women.

Participants in the BECT expended a total of 4174.9 (SD: 3286.1) calories/week, which included 2066.1 (SD: 1526.0) calories/week of low-intensity physical activity and 2106.6 (SD: 2438.6) calories/week of moderate-intensity physical activity. When stratified by sex, women had significantly ($p\leq 0.05$) lower total and moderate- to vigorous-intensity caloric expenditure/week compared to men. Intervention and control participants in the total and sex-stratified samples did not significantly differ in caloric expenditure/week. Participants in the BHS were generally less than active at baseline. Based on the 10,000 steps/day walking activity guidelines, 10.9% of participants were considered active. Based on the Department of Health and Human Services guidelines of 30 minutes of moderate-intensity activity/day, no participants met guidelines by completing three or more 10-minute bouts/day of 1000 steps/bout. Participants averaged 7729.0 (SD: 3506.1) total steps/day, which included 7015.1 (SD: 28350.5) steps at low-intensity and 713.9 (SD: 1011.0) steps at moderate- to vigorous-intensity. When stratified by sex, women had a marginally lower total walking activity at baseline ($p=0.18$). Intervention and control participants in the total and sex-stratified samples did not differ significantly on physical activity at baseline.

Intervention adherence

In the BECT EC intervention group, 79.8% of participants received the intervention (82.6% of women and 66.0% of men). Men and women differed significantly in intervention adherence ($p\leq 0.05$). The average number of intervention exposure hours in the study sample over the 2-year study was 589.4 hours (SD: 452.9). Men and women did not differ significantly in number of

exposure hours. BECT and BHS participants did not differ significantly in intervention adherence or number of intervention exposure hours

Intervention effects

Table 3 describes the sex-stratified impact of the intervention vs. control on caloric expenditure/week among BECT participants. We have exponentiated coefficient values for log-transformed variables below to indicate percent differences. At 12 months in women, there was a significant intervention effect in total caloric expenditure/week but not in low-intensity or moderate- to vigorous-intensity caloric expenditure/week; the intervention group averaged 16% less calories/week than the control group (0.84; 95% CI: 0.71, 0.98). At 24-months there was a significant intervention effect in moderate- to vigorous caloric expenditure/week but not in total or low-intensity caloric expenditure/week; the intervention group averaged -0.25 less kilocaloric expenditure/week (-0.25; 95%CI: -0.46, -0.40). At 12-months women in the intervention and control groups showed significant declines in caloric expenditure/week relative to baseline: the intervention group averaged 24% less total caloric expenditure/week, 16% less low-intensity caloric expenditure/week, and -0.27 less moderate- to vigorous-intensity kilocaloric expenditure /week (0.76; 95% CI: 0.67, 0.86 ; 0.84; 95% CI: 0.75, 0.95 ; and -0.27; 95%CI: -0.41, -0.12 respectively) and the control group averaged 13% less total caloric expenditure/week and 17% less low-intensity caloric expenditure/week (0.87; 95% CI: 0.76, 0.99 and 0.83; 95% CI: 0.73, 0.95 respectively). At 24-months women in the intervention and control groups also showed significant declines in caloric expenditure/week relative to baseline: the intervention group averaged 32% less total caloric expenditure/week, 27% less low-intensity caloric expenditure/week, and -0.40 less kilocaloric expenditure/week (0.68; 95% CI: 0.60, 0.77 ; 0.73; 95% CI: 0.64, 0.83 ; -0.40; 95%CI: -0.55, -0.24 respectively) and the control group averaged 27% less total caloric expenditure/week and 30% less low-intensity caloric expenditure/week (0.73; 95% CI: 0.63, 0.83 and 0.70; 95% CI: 0.62, 0.81 respectively).

At 12 months, men did not show any significant intervention effects across all caloric expenditure/week measures. At 24 months, men in the intervention group averaged 77% greater low-intensity caloric expenditure/week (1.77; 95% CI: 1.05, 2.94) than the control group. At 12 and 24 months, men in the control group showed significant decline in total caloric

expenditure/week relative to baseline: at 12 months, -0.39 less moderate- to vigorous intensity kilocaloric expenditure/week (-0.39; 95%CI: -0.68, -0.11), and at 24 months, 34% less low-intensity caloric expenditure/week and -0.53 less moderate- to vigorous-intensity kilocaloric expenditure/week (0.66; 95% CI: 0.46, 0.90 and -0.53; 95%CI: -0.84, -0.22 respectively).

Table 4 describes the sex-stratified impact of the intervention vs control on walking activity among BHS participants. At 12 months there were no significant intervention effects in women across all three walking activity measures (total, low-intensity, moderate- to vigorous-intensity). At 24 months, women in the intervention group averaged 1500.3 greater total steps/day (95% CI=77.6, 2922.9) and 1275.1 greater low-intensity steps/day (95% CI: 0.49, 2549.6) than women in the control group. Over the duration of the study, women in the intervention group maintained levels of physical activity similar to baseline. The women in the control group showed significant declines in total and low-intensity walking activity at 24 months. Compared to baseline, women in the control group declined by 1191.6 total steps/day (95% CI: -2243.7, -139.5) and 1275.1 low-intensity steps/day (95% CI: -1924.2, -73.1).

At 12 months, men in the intervention group averaged -1560 fewer moderate- to vigorous-intensity steps/day (-1560; 95%CI: -3000, -110) (note coefficients rescaled from table) and at 24 months averaged 1440 fewer moderate- to vigorous-intensity steps/day (-1440; 95%CI: -2800, -90) than men in the control group. There were no intervention effects across all other walking activity measures, and intervention and control groups also showed no significant declines at 12 and 24 months, compared to baseline levels, across all measures.

Discussion

In this study, we described the effect of the Experience Corps intervention on physical activity, including self-report physical activity and objectively measured walking activity. Considering self-report physical activity, men, but not women, in the intervention group showed increased caloric expenditure/week – specifically within the low-intensity range – at 24 months compared to their sex-matched controls. Men in the intervention group maintained physical activity levels, compared to baseline, over 12 and 24 months while men in the control group declined significantly, compared to baseline, at 12 and 24 months. Women in the intervention and control

groups on the other hand showed significant declines in caloric expenditure/week across intensity at 12 and 24 months. Additionally the control group showed increased total caloric expenditure/week at 12 months and increased moderate- to vigorous-intensity caloric expenditure/week at 24 months compared to the intervention group. Considering objectively measured walking activity, we found that over a 24 month period women, but not men, in the intervention group showed increased total and low-intensity steps/day compared to their sex-matched control group. Additionally, while women in the intervention group maintained walking activity levels over 24-months, women in the control group declined significantly in walking activity at 12 and 24 months. In men, the intervention group showed lower moderate- to vigorous-intensity steps/day at 12 and 24 months compared to the control group, and both intervention and control groups maintained walking activity across measures throughout the duration of the study.

Physical activity has been shown to be protective against a number of adverse health outcomes^{17, 62}; however, physical activity declines with older age²⁰. These declines are particularly concerning among older adults of low SES who have limited access to infrastructure and resources that encourage increased exercise and other forms of physical activity^{27, 63}. The results of this study indicate that a community-based intervention that naturally integrates activity in urban areas may effectively increase low-intensity walking activity in women and perhaps in men, but it may not increase moderate- to vigorous-intensity physical activities and affect natural declines in exercise-related and other higher intensity physical activities. These findings provide a template for designing successful interventions that may modestly encourage modest increases in physical activity and support those at highest risk for both inactivity and adverse cognitive and physical health outcomes⁶⁴.

Older adults within this study were mostly non-active by traditional standards for physical activity. At baseline, very few met estimated physical activity guidelines, and the majority of daily walking activity was within the low-intensity range. Although current physical activity guidelines focus on moderate-intensity physical activity⁶⁵⁻⁶⁷, older adults with a high number of chronic conditions and who live in environments that do not promote physical activity have great difficulty achieving those guidelines⁶⁸. For these older adults, a modestly more active lifestyle may be beneficial^{57, 69-73}. This study suggests that EC is an effective, long-term physical activity intervention that is

accessible and attractive to sedentary, underserved older adult populations. Additionally, the study emphasizes the importance of objectively measuring and identifying meaningful metrics of daily physical activity, particularly in non-active older adults for whom the majority of activity is in the low-intensity range. These activities may be related to daily functional and social activities that are difficult to capture without objective physical activity measurement tools ^{57, 74}.

Study results indicated intervention-specific effects for walking activity in women outside the program. Prior research suggests that EC is a pathway to other productive social and civic activities; after joining EC volunteers may start new work, volunteer, community, and educational activities ⁷⁵. Therefore increased walking activity measured in this study may be associated with those new activities. We can hypothesize that the mechanism explaining this increased extra-program activity may be the result of increased social, cognitive, and physical activity ³⁵ occurring within the schools. The EC intervention may have increased physical and cognitive capability, or behavioral motivation, which led to increased activity outside the program. The lack of an intervention effect at 12-months may be expected considering prior evidence suggesting that the rewards and benefits of the EC intervention may only occur after a period of acclimation to the school setting ⁷⁶.

Study results additionally indicated declines in caloric expenditure/week in women at 12 and 24 months as well as reduced caloric expenditure/week in the intervention compared to the control at 12 and 24 months. The decline in caloric expenditure/week may be expected considering that the version of CHAMPS used in the BECT was developed to capture exercise-related physical activities; age-related declines in physical activity generally ²², including declines in maximal aerobic capacity ⁷⁷ and resting metabolic rate particularly in sedentary older women ⁷⁸, is expected. It is important to note that the negative intervention effect was not found in low-intensity caloric expenditure/week but rather in total caloric expenditure/week at 12 months and moderate- to vigorous at 24 months. The negative intervention effect at 12 months may be due to acclimation to the school setting mentioned above. During the school year, volunteering in EC may replace or reduce the frequency or duration of participation in other physical activities. The CHAMPS measures physical activities over the last 4 weeks and did not explicitly discriminate between in and out of intervention activities, and therefore it may be expected to observe a short-term decline in physical activity within the intervention group. The negative effect at 24 months

may also be expected because while EC may increase low-intensity physical activity, EC and other lifestyle physical activity interventions may not be expected to have an effect on moderate- to vigorous-intensity physical activity.

Study results of self-report physical activity contradict those of objective walking activity. There are two potential explanations for this discrepancy. First, the mode of data collection for CHAMPS and SAM varied. As mentioned previously, the CHAMPS is a self-report physical activity questionnaire that focused mainly on exercise-related physical activities. Low-intensity physical activities specifically may be difficult to measure with self-report questionnaires often because it may be difficult to assess physical activities that may be related to function and social activities^{57, 74}. The lack of an intervention effect for low-intensity caloric expenditure/week may be due to measurement issues rather than a true contradiction with findings for walking activity. The SAM is an objective physical activity measure that may more sensitively capture low-intensity physical activities. Second, the study design for CHAMPS and SAM data collection varied. The CHAMPS questionnaire used in the BECT did not discriminate between within EC and outside of EC physical activities, while the BHS study design explicitly used the SAM to measure walking activity outside the program. While generally evaluations for the BHS and the BECT were scheduled during the summer and early fall after the end of the academic year, this design difference may contribute to differential results.

Intervention effects were sex specific. Other than a positive intervention effect in low-intensity caloric expenditure/week in men at 24-months, across both self-report and objective measures, there were no intervention effects in men, and intervention and control arms did not show any change at 12 and 24 months relative to baseline. Women, however, showed significant declines in physical activity and a negative intervention effect according to self-report measures, and significant positive intervention effects at 24-months according to objective measures. There are several potential explanations for these sex differences. First, at baseline men in this study were healthier than women considering socio-demographic characteristics including income and education, chronic disease burden including BMI, and physical activity measured by both self-report and objective measures. We may therefore expect more significant declines in physical activity in women over two years than men because they were at higher risk for physical and cognitive function decline at baseline. Considering positive intervention effects in women

observed in the BHS (objective measures), prior research has shown that physical activity interventions, particularly those like EC that may target lower-intensity, non-exercise activities, may be more effective for more sedentary and at-risk individuals ³⁹. Second, men had lower adherence to the Experience Corps intervention than women. In the BECT, 34.0% of men in the intervention group included in the analysis dropped out of the EC intervention prior to placement in the schools, compared to 17.5% of women. This high percentage of attrition among men may have led to a dilution of the intervention and therefore a lack of a positive intervention effect, particularly within low-intensity walking activity. Third, despite oversampling for men in the BHS in order to allow for sex-stratification in analyses of objective walking activity, our power to detect differences in the male group was limited considering the small sample size.

Limitations and Strengths

This study has limitations. While we were able to test the intervention effect in an RCT with a long follow-up, the male group within the sex-stratified sample was small. Additionally, the CHAMPS questionnaire used in the BECT was not well designed to capture non-exercise, low-intensity physical activities. Considering SAM data collection with the BHS, most participants provided less than seven days of data because of data collection protocol developed to minimize participant burden ⁵⁷. Best practices suggest that a seven-day protocol that includes weekday and weekend activity may be best to estimate physical activity ^{79, 80}. The study also had variable exposure and drop out from the intervention that may biased estimates of intervention effects. Finally, while the study sample represented an understudied, at-risk segment of the older adult population, a trial of high-intensity volunteer service may select for the more health conscious and physically active members of the community ^{81, 82}.

This study has a number of strengths. We implemented an analytic design where initial treatment assignment, rather than treatment compliance, was used evaluate the effect of the intervention. Thus results of the study may be conservative, and the positive intervention effect in women provides powerful evidence for the benefits of EC as a low-intensity physical activity intervention. We additionally relied on two different modes of physical activity data collection including self-report as well as objective measures that circumvent some of the bias associated with self-report. The objective measures may be more sensitive to activities within the low-intensity range that

may be more common in sedentary older adult populations^{57, 74, 83}. Finally, we explored the effects of a physical activity intervention within an underserved population including a substantial number of ethnic/racial minorities and individuals with low income who are not typically engaged in physical activity promotion interventions.

Conclusions

EC Baltimore was designed to attract a diverse population of older adults at elevated risk for both inactivity and adverse health outcomes. These older adults who may not engage in typical exercise and other health promotion interventions were recruited based on their desire to be generative, or “give back” to their community. This study provides compelling evidence for a community-based model of health promotion that, through modest increases in physical activity, may address disparities in health in an at risk population of older adults.

Figure 1: CONSORT diagram summarizing flow of participants through the Baltimore Experience Corps Trial (BECT)

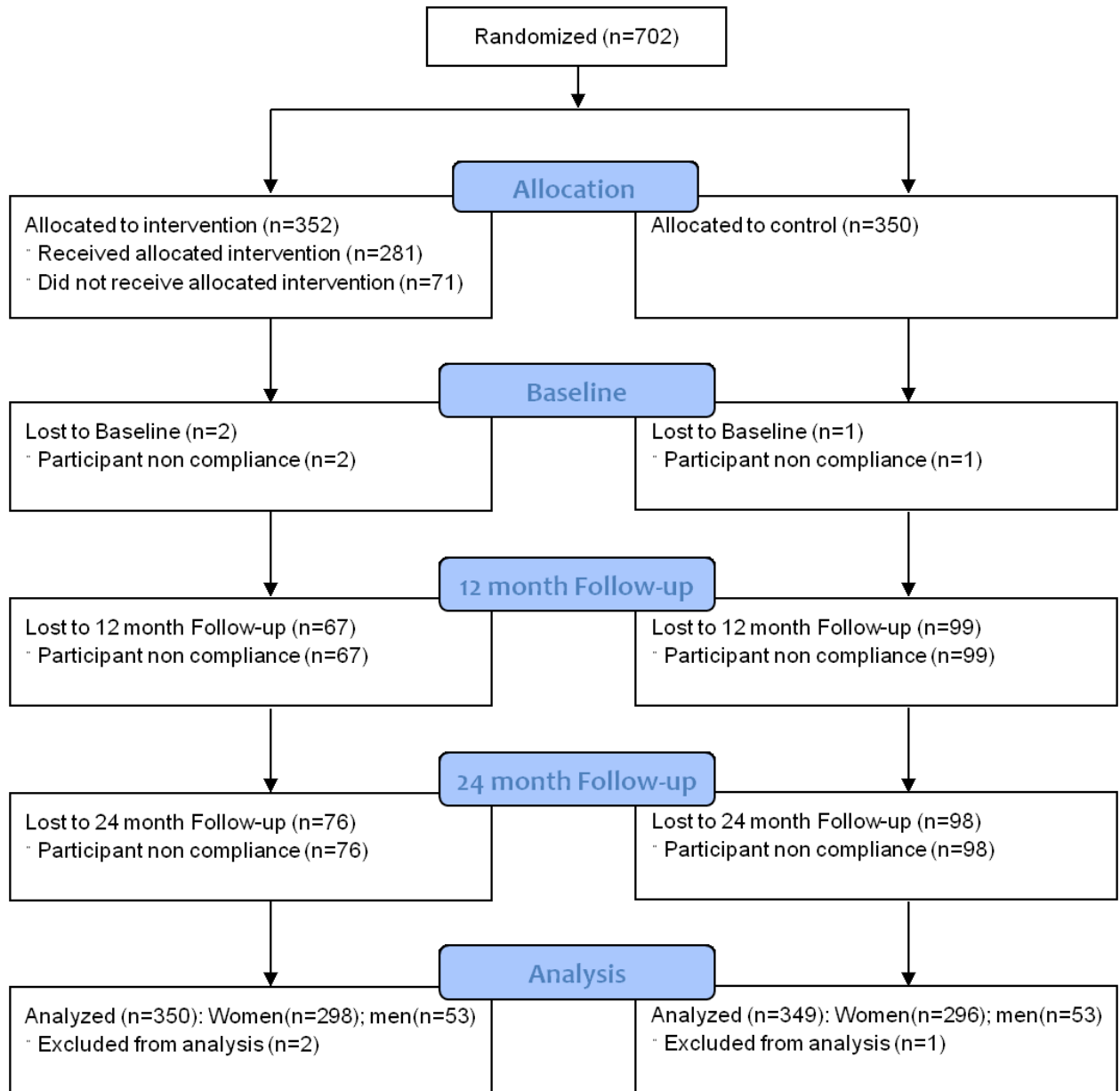


Figure 2. CONSORT diagram summarizing flow of participants through the Brain Health Study (sub study within the larger Baltimore Experience Corps Trial)

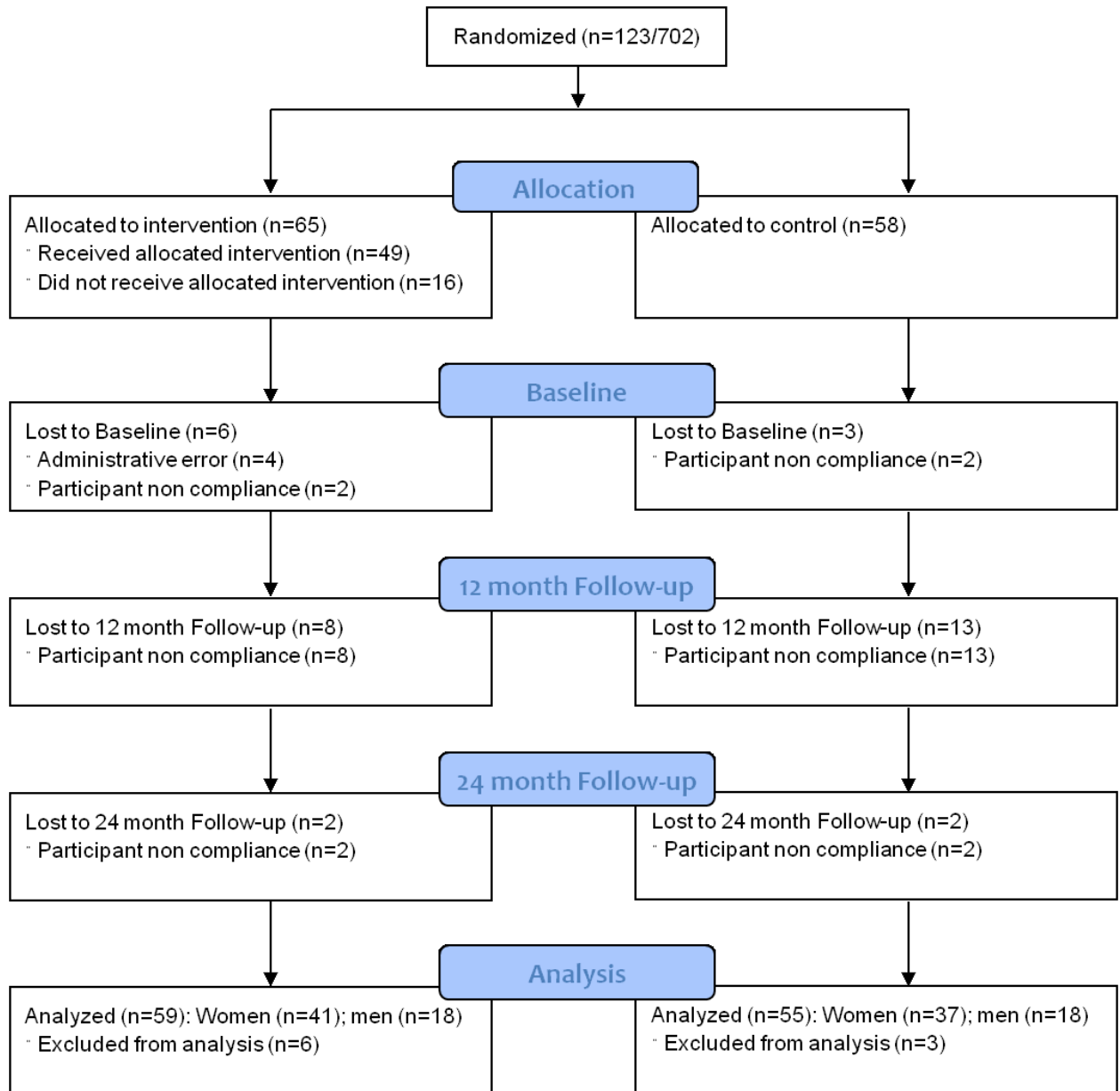


Table 1. Baseline characteristics of Baltimore Experience Cops Trial (BECT) participants

Characteristic	Total (n = 700)	Sample	Allocation Group	
			Experience Corps (n = 350)	Control (n = 349)
	Mean (SD) or N (%)		Mean (SD) or N (%)	Mean (SD) or N (%)
Age (years)	67.4 (5.9)		67.4 (5.9)	67.4 (5.8)
Sex (women)	594 (84.8)		298 (84.9)	296 (84.8)
Race (African American)	633 (90.4)		314 (89.5)	319 (91.4)
Education (\leq high school)	298 (43.4)		150 (44.0)	148 (42.9)
Income ($<$ \$15,000)	204 (29.2)		104 (29.7)	100 (28.7)
Health and Functioning				
Chronic Diseases				
Obesity (BMI \geq 30)	398 (56.9)		196 (55.8)	202 (57.9)
Hypertension	495 (73.8)		245 (72.5)	250 (75.1)
Diabetes	213 (31.7)		100 (29.5)	113 (33.9)
Global Cognition (MMSE)	28.1 (1.6)		28.1 (1.6)	28.1 (1.5)
Activity metrics				
<i>CHAMPS</i>				
Total caloric expenditure/ week	4174.9 (3286.1)		4199.5 (3511.2)	4150.2 (3047.9)
Low-intensity caloric expenditure/ week ^a	2066.1 (1526.0)		2072.0 (1567.1)	2060.2 (1485.6)
Moderate- to vigorous-intensity caloric expenditure/ week ^b	2106.6 (2438.6)		2127.4 (2601.1)	2085.3 (2267.1)
Intervention				
Intervention adherence	-		281 (79.8)	-
Total exposure hours over 24 months	-		589.4 (452.9)	0

SD, standard deviation; MMSE, Mini Mental State Exam; BMI, Body Mass Index; CHAMPS, Community Health Activities Model Program for seniors (self-report questionnaire)

Note: In the total sample, women had significantly lower total and moderate- to vigorous-intensity caloric expenditure/ week ($p < 0.01$), greater BMI ($p < 0.01$), lower income ($p < 0.05$), lower education ($p < 0.01$), larger percentage African American ($p < 0.05$), and greater total exposure hours over 24 months. Intervention and control groups did not significantly differ ($p \leq 0.05$) on any measures other than exposure; when stratified by sex, intervention and control groups differed significantly ($p < 0.05$) by age, education, and hypertension in men.

^a low-intensity activity measured by CHAMPS includes activities with metabolic equivalent (MET) values < 3.0

^b moderate- to vigorous-intensity activity measured by the CHAMPS includes activities with MET values ≥ 3.0 .

Table 2. Baseline characteristics of Brain Health Study (sub study within the larger Baltimore Experience Corps Trial) participants.

Characteristic	Total (n = 114)	Sample	Allocation Group	
			Experience Corps (n = 59)	Control (n = 55)
	Mean (SD) or N (%)		Mean (SD) or N (%)	Mean (SD) or N (%)
Age (years)	67.4 (6.0)		67.8 (6.2)	66.8 (5.7)
Sex (women)	78 (68.4)		41 (69.5)	37 (67.3)
Race (African American)	104 (91.2)		53 (89.8)	51 (92.7)
Education (\leq high school)	40 (35.4)		21 (35.6)	19 (35.2)
Income ($<$ \$15,000)	34 (29.8)		13 (22.0)	21 (38.2)
Health and Functioning				
Chronic Diseases				
Obesity (BMI \geq 30)	65 (57.0)		30 (50.9)	35 (63.6)
Hypertension	81 (71.7)		44 (74.6)	37 (68.5)
Diabetes	34 (30.1)		15 (25.4)	19 (35.2)
Global Cognition (MMSE)	28.4 (1.5)		28.4 (1.5)	28.3 (1.5)
% meeting physical activity guidelines				
10,000 steps/day ^a				
Active (\geq 10,000 steps/day)	11 (10.9)		6 (11.5)	5 (10.2)
30 minutes of moderate intensity activity ^b				
Active (\geq 30 minutes/day)	0 (0.0)		0 (0.0)	0 (0.0)
Activity metrics				
SAM				
Total steps/day	7729.0 (3506.1)		7626.1 (3684.4)	7838.2 (3341.1)
Low-intensity steps/day	7015.1 (28350.5)		6947.4 (3006.3)	7087.0 (2660.6)
Moderate- to vigorous-intensity steps/day	713.9 (1011.0)		678.7 (1069.0)	751.2 (955.2)
Intervention				
Intervention adherence	-		46 (78.0)	-
Total exposure hours over 24 months	-		576.4 (456.7)	0

SD, standard deviation; MMSE, Mini Mental State Exam; BMI, Body Mass Index; SAM, step activity monitor; BHS, Brain Health Study; BECT, Baltimore Experience Corps Trial

Note: In the total sample, women had significantly greater BMI ($p < 0.05$), marginally lower amount of walking activity ($p = 0.18$), and significantly greater intervention adherence ($p < 0.05$) compared to men. Intervention and control groups did not significantly differ ($p < 0.05$) on any measure other than exposure; when stratified by sex, intervention and control groups did not differ significantly other than BMI in women. BHS participants did not significantly differ ($p < 0.05$) from participants in the BECT on any measure other than gender (the BHS oversampled for men).

^a 10,000 steps/day considered an estimate of daily recommended walking activity

^b 30 minutes/day of moderate intensity activity (≥ 100 steps/min) considered an estimate of daily recommended walking activity

Table 3. Impact of the Experience Corps Intervention vs. Control on caloric expenditure/week among Baltimore Experience Cops Trial (BECT) participants

			Women		Men	
			12-month	24-month	12-month	24-month
			B (95% CI)	B (95% CI)	B (95% CI)	B (95% CI)
<i>Total caloric expenditure/week (log calories)</i>						
Intervention	effect:		-0.18	-0.11	0.05	0.37
Intervention – Control			(-0.35, -0.02) *	(-0.28, -0.05)	(-0.44, 0.54)	(-0.13, 0.88)
Intervention: change from baseline			-0.28 (-0.40, -0.15) **	-0.39 (-0.51, -0.26) **	-0.26 (-0.61, -0.10)	-0.24 (-0.60, 0.12)
Control: change from baseline			-0.14 (-0.28, -0.01) *	-0.32 (-0.46, -0.19) **	-0.11 (-0.46, 0.24)	-0.42 (-0.78, -0.06) *
<i>Low-intensity caloric expenditure/week (log calories)</i>						
Intervention	effect:		-0.07	-0.05	-0.14	0.56
Intervention – Control			(-0.24, 0.10)	(-0.22, 0.12)	(-0.36, 0.64)	(0.05, 1.08) *
Intervention: change from baseline			-0.18 (-0.31, -0.05) **	-0.32 (-0.45, -0.19) **	-0.23 (-0.63, 0.18)	-0.14 (-0.56, 0.27)
Control: change from baseline			-0.19 (-0.32, -0.05) **	-0.34 (-0.48, -0.21) **	0.05 (-0.35, 0.45)	-0.29 (-0.71, 0.12)
<i>Moderate- to vigorous caloric expenditure/week (kilocalories)</i>						
Intervention	effect:		-0.20	-0.25	-0.06	-0.12
Intervention – Control			(-0.40, 0.01)	(-0.46, -0.04) *	(-0.54, 0.43)	(-0.38, 0.63)
Intervention: change from baseline			-0.27 (-0.41, -0.12) **	-0.40 (-0.55, -0.24) **	-0.25 (-0.53, 0.03)	-0.20 (-0.49, 0.09)
Control: change from baseline			-0.05 (-0.20, 0.09)	-0.13 (-0.28, 0.02)	-0.39 (-0.68, -0.11) **	-0.53 (-0.84, -0.22) **

CI, confidence interval; MET, metabolic equivalent; * p<0.05, **p<0.01

Note: all models included covariates age at baseline and race; men-only model additionally included education and hypertension at baseline; total and low-intensity caloric expenditure/week were log transformed to a normal distribution and modeled using linear mixed models; moderate- to vigorous-intensity caloric expenditure/week was expressed as kilocalories (scaled by 1000) to allow for model convergence, had a negative binomial distribution, and was modeled using negative binomial regression models.

Table 4. Impact of the Experience Corps Intervention vs. Control on walking activity at 12- and 24-months among Brain Health Study (BHS) participants

	Women		Men	
	12-month	24-month	12-month	24-month
	B (95% CI)	B (95% CI)	B (95% CI)	B (95% CI)
<i>Total steps/day</i>				
Intervention effect:	-323.5	1471.2	-1550.1	-2378.3
Intervention – Control	(1739.7, 1092.6)	(60.3, 2882.0) *	(-4250.1, 1150.0)	(-5226.3, 469.6)
Intervention: change from baseline	-591.0 (-1601.7, 419.7)	298.8 (-680.8, 1278.3)	-1245.5 (-2739.0, 248.0)	-848.3 (-2610.3, 913.7)
Control: change from baseline	-282.9 (1292.4, 726.7)	-1187.8 (-2239.3, -136.3) *	-1143.3 (-2841.1, 554.5)	82.1 (-1683.3, 1857.6)
<i>Low-intensity steps/day</i>				
Intervention effect:	-43.4	1262.9	-796.5	-1417.3
Intervention – Control	(-1311.1, 1224.3)	(-0.13, 2526.0) *	(-2616.2, 1323.2)	(-3661.0, 826.3)
Intervention: change from baseline	-396.9 (-1285.8, 492.0)	307.0 (-554.7, 1168.6)	-757.0 (-1973.2, 459.2)	-532.6 (-1966.0, 900.8)
Control: change from baseline	-394.1 (-1281.5, 493.4)	-996.5 (-1921.5, -71.4) *	-597.3 (-1978.3, 783.8)	248.0 (-1193.7, 1689.7)
<i>Moderate- to vigorous-intensity steps/day</i>				
Intervention effect:	-0.35	0.29	-1.56	-1.44
Intervention – Control	(-0.93, 0.23)	(-0.32, 0.90)	(-3.00, -0.11) *	(-2.80, -0.09) *
Intervention: change from baseline	-0.30 (-0.77, 0.16)	-0.16 (-0.60, 0.28)	-1.11 (-2.25, 0.02)	-0.55 (-1.70, 0.59)
Control: change from baseline	0.09 (-0.38, 0.55)	-0.42 (-0.95, 0.11)	-0.65 (1.53, 0.22)	-0.21 (-1.01, 0.60)

CI, confidence interval; * p<0.05

Note: all models included covariate age at baseline; women-only model additionally included body mass index (BMI) at baseline. Total and low-intensity steps/day had a normal distribution and were modeled using linear mixed models; moderate- to vigorous-intensity steps/day was scaled by 1000 to allow for model convergence, had a negative binomial distribution and was modeled using negative binomial regression models.

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Chapter 7.

Aim 3: Physical activity and physical function: development of biometric signals to predict cognitive decline and disability

Introduction

The relationship between the central nervous system (CNS) and physical movement has been studied extensively in animal models. These rigorously controlled experiments indicate that physical movement in an environment is intimately connected to the CNS at the level of molecules, neurons, signaling pathways, and behavior ¹. Evidence from studies in patient populations with neurologic disorders additionally indicate that the CNS is an important contributor to mobility and lower extremity physical function ². In community-dwelling, older adult populations free of neurologic disorders, in addition to the development of clinically diagnosable gait abnormalities ^{3,4}, age associated declines in physical activity and lower extremity function are common ⁵⁻¹⁰. Evidence indicates that abnormalities in mobility and physical function are risk factors for cognitive decline, MCI, and dementia ¹¹⁻¹³; and impaired cognition is also a risk factor for mobility limitations, falls, and physical function abnormalities ¹⁴⁻¹⁷. These findings suggest that the CNS and physical movement are closely linked and at least partially dependent on the other, and abnormalities in both may be associated with a common underlying pathophysiology ¹⁴. This additionally suggests that measures of physical movement may have important utility in predicting future cognitive decline.

Physical movement, which includes a broad range of concepts and measures including physical activity, physical function, and physical fitness, can be considered a biometric signal of cognitive decline. Although these measures have been shown to be associated with cognition ²⁰⁻²⁵, and are often used interchangeably, they are conceptually different. Understanding the relationship among them is essential to understanding the mechanistic or biologic relationship between physical movement and the CNS and developing appropriate biometric signals to predict cognitive decline.

Below we define terms and expand on the relationship among them particularly considering older adult populations and models of disability.

Definitions

Physical activity includes any activity that requires movement and an increase in energy expenditure above a resting level ^{26, 27}. As described in Figure 1, physical activity can be considered “What” an individual is doing. Physical activity is composed of three subdomains: non-exercise

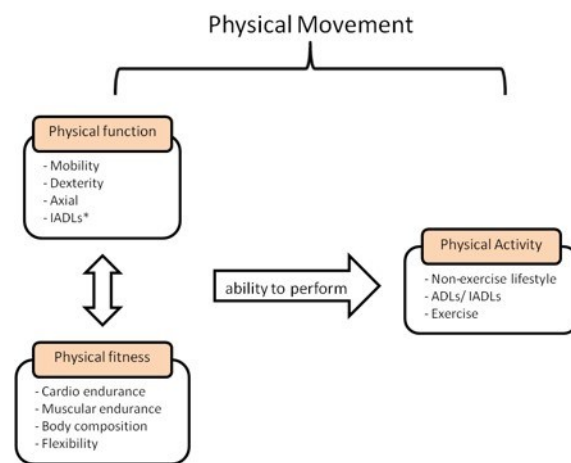


Figure 1. Relationship among various measures of physical movement: physical function, physical fitness, and physical activity

leisure-time/ lifestyle activities (e.g., walking, gardening); activities of daily living (ADL; e.g., eating, bathing)/ instrumental activities of daily living (IADL; e.g., shopping, housework), and exercise (lifting weights, running) ^{28, 29}.

Physical function is the ability to carry out an activity that requires physical capability ⁺⁺⁺, and is composed of four subdomains: mobility (lower extremity function), dexterity (upper extremity function), axial (neck and back function), and ability to carry out IADLs ^{+++ 30}.

Physical function can be considered the ability to carry out physical activities (Figure 1), and includes the full spectrum of physical functioning from severe impairment to exceptional physical ability.

Physical fitness is “a set of attributes that that people possess or achieve” ^{§§§} and relates to the ability to perform physical activities (Figure 1) ³¹. Physical fitness includes four sub domains: cardiorespiratory endurance, muscular endurance, body composition, and flexibility ^{28, 32}. Physical fitness and physical function are similar terms; physical fitness is typically used when considering standards/ guidelines in youth and adults, and is often focused on physical activities related to exercise ³³. Physical function is typically used when considering older adults and the disablement process, and often focuses on the physical activities related to IADLs ³⁴.

Conceptual Frameworks

⁺⁺⁺ As defined by the NIH Patient Reported Outcomes Measurement Information System (PROMIS)

⁺⁺⁺ The inclusion of IADLs in the definition of physical function comes from an inaccurate use of term. For the purposes of this discussion, IADLs are considered physical activities, NOT physical function.

^{§§§} As defined by the American College of Sports Medicine

The relationship between physical function/ fitness and physical activity is often assumed. One real-world example that clearly demonstrates this assumption is the National Football League (NFL) scouting combine. This week long testing session is used to evaluate potential NFL players; players perform a series of physical fitness tests including the 40 yard dash and 225 lb. bench press to failure (tests of cardiovascular and muscle endurance) and the Cybex test (flexibility and stability)³⁵. The results are used to determine draft status (whether and when players are chosen by an NFL team) and have a significant impact on salary and the career of potential NFL players. NFL coaches consider physical fitness scores when drafting players because they believe that those scores are associated with actual performance on the football field. For example, the results of the 40 yard dash and bench press to failure in the combine are assumed to be associated with the success (i.e., number of completed receptions) of a wide receiver in the NFL. Relevant to our conceptual framework, the physical fitness scores players achieve in the combine (i.e., the “lab”) are considered predictive of, or associated with, actual physical activities on the field (i.e., the “real world”). Although some evidence indicates that this association is generally correct³⁶, there is contrary evidence³⁷ suggesting that while the combine may measure fitness, fitness in itself may not be an appropriate proxy for “football playing ability.” Successful performance on the field may require multiple physical and mental skills that are not well tested by the narrow focus of the skill specific tests used in the combine.

A conceptual scheme for understanding the relationship between physical function/ fitness and physical activities is “could do” (capacity) and “do do” (actual behavior). This scheme was first mentioned by Verbrugge and Jette in their seminal paper, *The Disablement Process*³⁸ and then developed in detail by Glass ****³⁹. The disablement process is a pathway from pathology (damage – e.g. cellular or tissue – due to disease) to impairment (loss or abnormality in function due to pathology) to functional limitation (inability to perform a task) to disability (the “gap between capability and environmental demands”⁴⁰)^{38,41}. Measures of function are typically used to place individuals on the disability pathway. In aging research, function or functional status are related to ADLs and IADLs⁴². Living independently requires accomplishing these essential activities, and therefore they are considered the standard for determining disability incidence and

**** Glass considered three tenses of functioning: “can do” (hypothetical); “could do” (experimental); and “do do” (enacted). Because of our focus on performance-based measures, we consider only “could do” (physical capacity measured in the lab) and “do do” (physical performance measured in the real world).

prevalence. Maintaining these functional activities is also considered an important outcome for health interventions. Function can be measured using self-report or performance-based tests (see additional detail in Measurement section below), and – as described by Glass – can be determined by considering the experimental context, or “could” you accomplish a particular functional task, and the enacted context, or “do” you accomplish that task.

While Glass was primarily concerned with discordance between what individuals report being able to do versus what individuals report doing, one can naturally extend his concepts to understand the relationship between physical function and physical activity. Performance-based measures of physical function (and fitness) are related to capacity, or whether an individual could carry out an activity within a laboratory context. Performance-based measures of physical activity are related to the actual behavior, or whether an individual does carry out an activity. Similar to the NFL example, consider IADL shopping (without the use of assistive devices). The physical components of shopping, including walking up and down the aisles and grabbing groceries, can arguably be measured in the lab using standardized, performance-based measures of mobility and dexterity. Performance on those tests can be considered a proxy for or associated with actual performance of (or ability to perform) that activity in the real world.

Below we summarize standard measures of physical function and physical activity used in epidemiologic research with particular focus on performance-based measures. Because of our focus on aging, we do not discuss measures of physical fitness, which have been reviewed extensively elsewhere^{43, 44}. Although certain measures of fitness are used in studies of older adults (e.g., maximal oxygen consumption (VO2 max) and forced expiratory volume (FEV)), the majority of relevant measures are included within the physical function domain. After the Measurement section, we continue to explore the relationship between physical function and physical activity, specifically considering differences inherent to the experimental and enacted context and the disablement model.

Measurement

Physical Function

The assessment of physical function was first used in a clinical setting in the 1920s^{45, 46}, and became a standard component of clinical evaluations of older adults in the 1950s⁴². Katz et al. developed the first standardized, graded ADL scale based on a group of patients with hip fracture; the scale ranked patients from A through G – indicating adequacy of performance – on six functions: bathing, dressing, going to the toilet, transferring, continence, and feeding^{42, 47}. Since the first IADL scale, well over 40 self-report IADL scales have been developed. These scales and theory are discussed at length elsewhere^{48, 49}.

Performance-based measures of physical function can be defined as assessor/ evaluator determined, objective measures of standardized functional tasks⁴⁵. These measures began to enter the mainstream of epidemiologic and clinical research methods in the 1980s as researchers began to identify limitations of self-report physical function measures including reproducibility, sensitivity to change, ceiling effects, and socio-cultural biases^{45, 49}. Researchers additionally recognized that decline in function may precede conscious recognition (i.e., self report of loss of function), and therefore it may be possible to identify “preclinical disability”⁵⁰ using performance-based tests⁵¹.

Even prior to the 1980s, researchers understood that with performance-based measures of physical function the implicit assumption was that “complex...movements used in daily activities [could] be reduced to certain patterns” that could be tested in a standardized way⁵². Additionally, as described by Carroll in his 1965 paper, *A Quantitative Test of Upper Extremity Function*, performance-based measures of physical function 1) need to “have a direct relationship to what the patient is able to do in every-day activities...” and 2) be “simple and quick enough to be carried out in an outpatient department or office by the doctor or technician.”⁵² In order to accomplish this, a number of groups began developing performance-based tests that varied from simulating IADLs⁵²⁻⁵⁴ to more standardized tests that measured general domains of physical function^{45, 55, 56}. The physical performance test (PPT) developed by Reuben et al, is one of the most commonly used IADL simulation tests; the 7-item test consists of the following tasks: writing a sentence, simulated eating, lifting a book to a shelf above shoulder level, putting on a jacket, picking up a penny from the floor, turning 360 degrees, and walking 50 ft⁵³. Performance is based on time to complete (other than the 360 degree turn). The short physical performance battery (SPPB) developed by Guralnik et al, is one of the most commonly used standardized, general lower

extremity physical function tests ⁵⁶. This 3-item test consists of the following tasks: tests of standing balance including tandem, semi-tandem, and side-by-side tasks, walking on an 8 ft. course, sitting and rising from a chair. Similar to the PPT, performance is based on time to complete (other than standing balance); longer completion time is considered a proxy for greater difficulty completing the task. Other performance-based tests of complex or higher-order IADLs performed regularly by older adults include the Hopkins Medication Schedule ⁵⁷, which simulates medication management, and the Virtual Action Planning-Supermarket, a computer program that simulates grocery shopping ⁵⁸.

A relatively recent innovation in performance-based measures of physical function is the measurement of gait variability. Developed in the late 1990s by Hausdorff et al, (e.g. ⁵⁹), this measure uses force sensitive insoles placed in the subjects' shoes ^{60, 61} to measure gait parameters including gait speed, stride time, and stride length as well as variability in those parameters ⁵⁹. Gait mats have also been used by other research groups to measure similar parameters^{3, 62}. Gait variability has been shown to be a quantifiable feature of walking that is altered among individuals exhibiting pathology related to cognitive (neurodegenerative diseases) and physical function (e.g., falls and frailty) syndromes and decline ^{15, 59, 63, 64}.

Performance-based measures of physical function can be categorized into three types: 1) tests of whether the individual is able to perform the task or not (e.g., 360 degree turn, side-by-side stand, and semi-tandem stand); 2) tests where the individual is asked to perform the task at usual speed (e.g., usual gait speed, 6 minute walk); and 3) tests where the individual is asked to perform the task at maximum capacity (e.g., rapid gait speed, grip strength, FEV). While performance-based tests at capacity are typical of tests used for elite athletes where the actual real-world activity is being accomplished at full capacity, for tests of whether an individual may be able to complete ADLs or IADLs, the real-world task may not require an individual's full capacity, and therefore it may be more important that the individual performs the test task "normally." ⁶⁵ In the field of geriatrics, very little has been done to understand the relationship among these different types of tests; after the Measurement section we make an effort to conceptualize this in terms of the disablement model.

The main way performance-based tests of physical function have been validated is through construct validity (e.g. ^{53, 66}) Traditionally, researchers have considered physical activities of interest (e.g. IADL shopping) as unmeasurable in the real world other than through self-report. For example, we are generally unable to measure how an individual walks down an aisle in a grocery store and places groceries in a cart. While emerging wearable technology, as we argue later, may be changing this, performance-based tests of physical function can be considered an abstraction or proxy measurement of the unmeasured latent variable: performance-based physical activity in the real world. As argued by Guralnik et al., “The validity of any measure of functioning cannot be assessed directly, as a gold standard does not exist.” ⁴⁵ Therefore, construct validation has taken two forms: 1) testing the associations between performance-based measures of physical function and self-report physical function, and 2) testing the associations between performance-based measures and disability outcomes including frailty and mortality.

The associations between performance-based and self-report physical function are moderate ⁶⁷⁻⁶⁹, and discrepancies have been generally explained using the same rationale considered by researchers arguing for the inclusion of performance-based measures due to measurement limitations in self-report ⁴⁵. It is important to note, however, that performance-based measures are not simply better measures of physical function than self-report. Both are important and potentially different measures of function and functional disability. First, consider the primary discordant group of interest (similar to those identified by Glass ³⁹): those who may self-report the ability to perform a functional activity with minimal difficulty but may have performance-based scores that indicate difficulty. Outside of measurement error, the discordant groups would only exist because the two measures are assessing conceptually different things.

In their paper exploring the natural history of functional loss prior to disability, Fried et al, defined

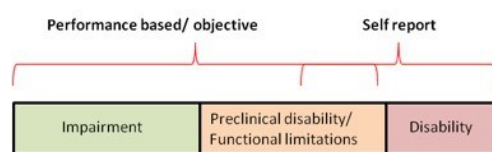


Figure 2. Measurement corresponding to different dimensions of the disablement model.

preclinical disability as “...a state of early identifiable functional loss, occurring due to impairment, and which precedes recognition of difficulty with task performance.” ⁵⁰ Preclinical disability is similar to “Functional limitations,” described by Nagi et al. as a transition stage between impairment and disability ⁴¹.

Self-report can be considered a measure of conscious recognition of difficulty in functional task

or activity performance. As described in Figure 2, this measure is particularly useful for measuring, and sensitive to, disability; more novel self-report methods that ascertain modification of method and frequency of task performance ⁷⁰ may also be sensitive to late, preclinical disability. Performance-based measures may be considered useful for measuring impairment and preclinical disability, both dimensions that precede disability (Figure 2). These measures may be sensitive to a subclinical or subconscious state of disability characterized by a decline in function from “normal,” before that decline becomes conscious, clinically apparent, or interferes with reported function ^{50, 71}. Discordant groups where individuals self-report no difficulty, however, show identifiable functional loss in performance-based tests, and may be in a transition state in the disablement process. After the Measurement section, we discuss in detail the consideration of measures, and metrics derived from those measures, in terms of sensitivity to specific dimensions of disability or “locations” on the disablement pathway.

Physical Activity

Physical activities include anything an individual does that requires energy expenditure above a resting level ^{26, 27}. These activities are typically measured in terms of energy cost relative to rest. A metabolic equivalent (MET) is defined as 1kcal/kg/hr, or approximately the energy cost of sitting at rest ⁷². For example in older adults, walking for leisure/ pleasure is assigned an MET, or intensity value of 2.5 ⁷³. This indicates that walking requires 2.5 times the energy required to sit at rest. Activities can range in intensity from low (<3.0 METS) to moderate to vigorous (≥3.0 METS) ⁷⁴. Low-intensity activities include those related to standing and casual walking and are typically within the non-exercise and IADL domains. Moderate- to vigorous-intensity activities typically involve moderate to large increases in breathing and heart rate, and are typically within the exercise domain. It is important to note that energy expenditure and physical activity are not synonymous. Energy expenditure depends on fitness, gender, age, and body mass and therefore is an indirect measure of physical activity ⁷⁵ that is necessarily biased particularly when measured with self-report within heterogeneous populations.

Physical activity guidelines were developed based on evidence indicating that aerobic activities drive improved health outcomes ⁷⁶. The primary recommendations state that healthy adults “need moderate-intensity aerobic (endurance) physical activity for a minimum of 30 minutes on

five days each week or vigorous-intensity aerobic physical activity for a minimum of 20 minutes on three days each week ^{29, 76, 77}. The activity dose (30 min/ 20 min) is based on thresholds of energy expenditure measured in METs ⁷⁶.

In many epidemiologic studies, self-report physical activity questionnaires are often used to measure physical activity. These questionnaires are often population specific, and estimate energy expenditure by 1) including the entire spectrum of physical activities a specific population may engage in; 2) ascertaining the frequency and duration of participation in those activities; and 3) calculating total energy expenditure per week or per month based on the METs assigned to each activity. For example, the Community Health Activities Model Program for Seniors (CHAMPS) questionnaire, developed specifically for older adults, includes low-intensity activities (e.g., walking for errands and light gardening) that older adults may typically engage in, and has adjusted MET values to better reflect the aerobic capacity of older adults ⁷³. Metrics derived from the questionnaire in addition to total caloric expenditure/week include frequency, type, and intensity of activity.

Objective measures of physical activity are defined as measures that provide repetitions of a unit amount of physical activity where that unit maintains its size (and allowable range of error) independent of who or what is being measured ⁷⁸. These measures include measures of energy expenditure and oxygen uptake; and assessments of real-world physical activity. “Gold standard” measures of oxygen uptake and energy expenditure, including calorimetry and doubly labeled water, have been discussed extensively elsewhere (e.g. ^{79, 80}); due to cost and the need for specialized equipment, these methods are rarely used in population-based studies and will not be discussed in detail here. Additionally these measures, while often used as measures of physical activity, are actually measures of physical function and fitness.

Objective measures of real-world physical activity are defined as measures that assess movement ^{****} from rest while an individual is physically active in their free-living environment. We

^{****} Heart rate monitors can also be considered measures of free-living physical activity. Heart rate is generally linearly associated with aerobic activity intensity; however it is a proxy measure that can also be affected by emotions, stress, etc. While these devices have been used successfully in population-based studies, we do not discuss these monitors in detail because they generally provide poorer data compared to accelerometers in measuring physical activity and energy expenditure.

specifically define these measures as performance-based measures of physical activity (compared to performance-based measures of physical function). The two main device categories used to measure physical activity in the real world are pedometers and accelerometers ⁷⁹. Within the last decade, use of these devices has increased exponentially in the research and commercial realms.

Pedometers are small motion sensors worn on the waist or ankle that measure walking activity typically by estimating number of steps walked. These devices estimate steps through a number of mechanisms including 1) a spring-suspended lever arm that is sensitive to vertical displacement; and 2) an accelerometer that measures acceleration in up to three orthogonal planes ⁸¹. Pedometers are not sensitive to weight-bearing activities, and typically do not account for variability in step length due to height and leg length differences ⁷⁹. Additionally, pedometers capture physical activity specific to walking, which necessarily excludes any non-ambulatory movement associated with trunk and upper body activities. Walking activity ^{****} is required of many activities adults and older adults complete, and is a significant component of all three subdomains of physical activity (non-exercise leisure-time activities/ lifestyle activities); ADL/ IADLs; and exercise). There is limited if any research quantifying what percentage of daily physical activity includes walking activity, and researchers often use walking activity as a proxy for physical activity and/or assume that it is linearly correlated with total physical activity.

Accelerometers are small motion sensors worn on the wrist, hip, or ankle that measure change in velocity by time across orthogonal axes. The two main types of accelerometer mechanisms are the piezoelectric effect and the capacitance sensor. The piezoelectric effect which is typical of most accelerometers, uses microscopic crystals sensitive to accelerative forces that produce a voltage when stressed. The capacitance sensor uses the sensitivity of capacitance change to accelerative force to produce a voltage ⁸². Accelerometers all use proprietary software to convert the accelerative force magnitude to physical activity metrics that range from activity counts and steps to METs. These metrics, despite interpretability issues ⁸³ are considered measures of physical activity associated with movement of the area of the body where the accelerometer is attached. Some evidence suggests that in healthy adults, placement on the wrist, hip, or ankle

^{****} Walking activity can be considered any activity that requires lower extremity mobility. This is different from walking, which is often used in terms of “walking for exercise” and included in many health guidelines particularly for older adults.

produces reliable data ⁸⁴, while other evidence suggests that placement may affect accuracy ⁸⁵. In general determining placement for the detection of physical activity depends on 1) the activities of interest (walking activity is best measured by attaching the motion sensor to the ankle ⁸⁶ whereas hip placement may be best for everyday activities ⁸⁵; 2) compliance (certain body locations may increase or decrease compliance depending on the demographics of the population of interest; and 3) importance of recognizing activity versus simply quantifying the amount, duration, or frequency of activity ⁸⁵.

Similar to the previous discussion about physical function, self-report and performance-based measures of physical activity are important and different measures of activity. Associations between both are low to moderate ⁸⁷, and discrepancies are partially related to measurement limitations in self-report. Troiano et al. published one of the more cited examples of this discrepancy. Using the 2003-2004 National Health and Nutritional Examination Survey (NHANES), the authors found that adherence to physical activity guidelines was far lower when using objective physical activity measures compared to self-report ^{5 §§§§}. Other studies have found the opposite association, that self-report under-estimated physical activity compared to objective measures ⁸⁷.

Again, considering the conceptual scheme developed by Glass ³⁹, the relationship between self-report and performance-based measures of physical activity can be considered in terms of the relationship between “do do” recalled by the individual and “do do” measured objectively. Individuals generally are able to recall moderate to vigorous intensity activities (including exercise) better than low-intensity activities (including housework, walking for errands, etc.) ^{88,89}. As argued by Lee and Shiroma, one of the reasons why physical activity guidelines in the United States do not include recommendations for low-intensity physical activity is because of this limitation in measurement for self-report physical activity questionnaires used in large-scale epidemiologic trials that underlie national guidelines ⁹⁰. For older adults, this is particularly important because the majority of activity is within the low-intensity range and a large percent of older adults report no moderate to vigorous-intensity activity ⁹¹⁻⁹⁴.

§§§§ The methods used by Troiano et al. included use of counts and count thresholds to determine moderate and vigorous activity. The appropriate thresholds to determine activity intensity (dependent on the type of accelerometer, placement, etc.) continues to be debated in the physical activity literature.

Self-report and performance-based measures of physical activity additionally measure different aspects of physical activity. In Figure 3 we describe the data collection and interpretation



Figure 3. Data collection and interpretation “pyramid” for performance based measures of physical activity vs. self-report.

“pyramid” that explains this difference in measurement⁹⁵. Performance-based measures quantify how much activity occurs in the real-world. This includes amount, duration, and frequency of physical activity^{26,96}. Pedometers and accelerometers are agnostic to activity; these motion sensors do not discriminate between types of activity (or “What”). Once how much activity is recorded, researchers can interpret the activity (or voltage) signals to determine what activity is occurring (e.g., running, sitting, walking, etc.). While still in its infancy in terms of use in public health and

population-based studies, activity recognition or detection using pattern recognition and various other data mining techniques is an emerging area in fields of computing, computer science, and statistics⁹⁷⁻⁹⁹. Self-report measures assess physical activity by first asking individuals what activity they are performing. This is the opposite of the “pyramid” for performance-based measures. While determining “what” is still an exploratory field for researchers using accelerometers, what activity individuals complete during a given period of time is the information that self-report questionnaires assess with the highest fidelity. After determining the type of activity, questionnaires attempt to measure how much – including amount, duration, and frequency – physical activity occurs.

Performance-based measures: relationship between physical function and physical activity

We now return to the conceptual frameworks that can help us understand the relationship between performance-based measures of physical function, which can be considered capacity or “could do,” and performance-based measures of physical activity, which can be considered what individuals actually do, or “do do.” Understanding the relationship between these measures first requires a broad understanding of the relationship between performance-based tests and the disablement model. Below we develop general concepts relating performance-based tests to the disablement model. We then return to research on physical movement and cognition,

considering life course research on cognition and progression of cognitive impairment as a model of how we can start to better understand physical function, physical activity, and disablement.

Performance-based measures and disablement

Disablement occurs through four general stages or dimensions: pathology, impairment, functional limitations or preclinical disability, and disability (Figure 4; ⁴¹). If we assume that it is possible to measure each of these dimensions using performance-based tests, then it is extremely important to understand 1) what type of test is it (see description in Measurement (Physical Function) section; 2) what the test measures (i.e., what are the test metrics); and 3) what dimension is the test most sensitive to ^{*****}. For example,

consider the turn 360 degrees test included in the PPT ⁵³. This is a performance-based measure of physical function that tests whether or not an individual can complete the task (*what type of test*); the test assesses dynamic balance, gait, and

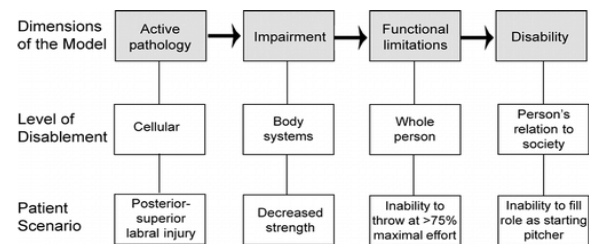


Figure 4. Nagi disablement model (figure reproduced from ¹)

lower extremity strength (*what the test measures*) ¹⁰⁰; and the test may be most sensitive to late preclinical disability, but not sensitive to measuring signs of pathology, impairment, or early preclinical disability (*what is the test most sensitive to*). Now consider a similar test where we ask an individual to turn 360 degrees five times at their usual pace on a force sensitive platform ¹⁰¹. This is a performance-based measure of physical function that tests an individual at their usual speed (*what type of test*); the test assesses the same lower extremity components as the previous test, but is specifically interested in gait variability measured by sway across multiple trials (*what the test measures*); and the test may be most sensitive to signs of impairment and preclinical disability, and can also be used to measure disability (*what is the test most sensitive to*). Finally, consider a similar test again where we ask the individual to complete five, 360 degree turns at their fastest pace. This is a performance-based measure of physical function that tests an individual's maximum capacity (*what type of test*); the test assesses similar components to the prior tests, but is specifically interested in time to complete (*what the test measures*); and the test

^{*****} In this discussion we do not include pathology as a dimension that can be measured by performance based tests. This dimension, which is at the cellular level of disablement (see Figure 4), may be better measured by blood and other biomarkers.

may be most sensitive to signs of impairment and may be unsafe to administer in populations that are either in the preclinical disability or disability stage (*what is the test most sensitive to*). Figure 5 provides a theoretical diagram of the relationship between the type of performance-based test and the dimension or stage of disability. Tests of capacity may be most sensitive to impairment, tests at usual speed may be most sensitive to late impairment and preclinical disability, and testing whether an individual is able to perform a task or not may be most sensitive to late preclinical disability and early disability.

Fitzpatrick et al.'s findings provide a compelling example of how the type of test (i.e., *what type of test*) may be differentially sensitive to different stages of disablement¹⁰². In an exploration of the cross-sectional relationship between gait speed and cognition in the Ginkgo Evaluation of Memory Study (GEMS), the authors found that fast-paced gait speed was strongly associated with cognition compared to usual-paced gait speed, a measure at usual speed, and difficulty with ADLs and IADLs, self-report measures of ability to perform or not¹⁰². Fast-paced gait speed is a performance-based measure of physical function that tests an individual's maximum capacity (*what type of test*) and assesses gait and functional mobility by time to complete (*what the test*

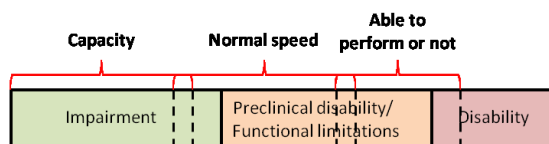


Figure 5. Sensitivity of three types of performance based physical function tests to the stage or dimension of disablement

measures). In their discussion of results, they explained that within the physically high functioning GEMS cohort, usual walk and self-report ADLs and IADLs may not have provided enough variability to separate individuals:

“Walking at self-selected usual pace may not have sufficiently stressed persons with lower physiologic reserve, and the additional effort needed for rapid-paced walking may have allowed differences in fitness and functionality to emerge.”¹⁰² Because the high functioning cohort used in this study may be within the early stages of disablement, including impairment or early preclinical disability, tests of capacity were the most sensitive compared to tests of usual speed or tests of ability to perform or not.

In addition to the type of test (*what type of test*), metrics (*what the test measures*) within a given type of test may also be differentially sensitive to different stages of disablement, and may reflect very specific physiologic processes occurring due to the disablement process. In his fascinating study of gait changes in older adults, Maki instructed participants to complete an eight meter walk

gait test while wearing instrumented exercise slippers (similar technology to the force sensitive insoles used by Hausdorff et al. described previously). The eight meter walk test is a performance-based measure of physical function that tests an individual at usual speed (*what type of test*) and assesses gait and functional mobility (*what the test measures (metrics)*). Maki collected various gait parameters from the test, including stride length, speed, and stride-to-stride variability. He additionally collected fear of falling data prior to the gait test and falls data weekly for one year following the test. Maki found that shortened stride length and reduced speed were associated with fear of falling but not falls, while increased stride-to-stride variability was associated with risk for falls but not fear of falling. These results suggest that certain stride metrics can be considered compensatory; individuals who feared falling altered their gait as a stabilizing adaptation. Other metrics may indicate subtler changes related to foot placement and center of mass displacement that are related to future falls ¹⁰³.

Maki's work indicates the importance of understanding the mechanistic or physiological process of pathologic gait changes, and the importance of developing sensitive metrics that are indicators of specific stages of that process and associated with specific outcomes. Again, considering the disablement model, if we clearly understand how gait changes across dimensions from pathology to disability, we can develop metrics from a performance-based test that may be sensitive to those dimensions. Maki hypothesized that as older adults age, fear of falling produces a compensatory gait change (e.g., slowed gait) that may increase stability and reduce falls, while increased variability may be an indication of general decline in motor balance and stability. If we map this on the disablement process, we can consider metrics such as slowed gait and shortened stride length as metrics related to an individual recognizing impairment or functional limitations and associated with fear of falling. These metrics may have an indirect relationship to actual impairment or functional limitations. Variability on the other hand is a general decline metric and may have a direct relationship to impairment and functional limitations and associated with falls, which is itself a risk factor for disability. If we believe that sub-conscious change may precede conscious change, we may be most interested in using data collection tools and metrics that may reflect the sub-conscious changes that are indicative of the earliest stages of disability. Figure 2 suggested that performance-based metrics may be more sensitive than self-report to early stages of disability. Metrics from performance-based tests may also vary in sensitivity to early stages and also vary in their relationship to sub-conscious and conscious change.

Lab vs. real world: relationship between performance-based measures of physical function and physical activity

Researchers from fields ranging from economics to psychology have used experimental models in laboratory settings to generate data meant to inform and explain the real world. The most important assumption in the collection of laboratory data is that the results can be extrapolated, or have a predictable (and “model-able”) relationship to the real world. Deviations from this assumption have been considered by many theorists.

Winkler and Murphy, in their paper exploring differences between laboratory and real world settings, consider conservatism in probability research as a way to understand these deviations¹¹². Conservatism can be considered the difference between how a subject may perform in a lab setting vs. how that subject may perform in the real world. The authors considered a Bayesian framework to understand how an individual may guess at the probabilities of particular poker chips in two different bags in a lab vs. how they would guess in the real world. In the lab setting, the individual is provided with a prior, or the probability that a particular bag (vs. the other bag) may have a particular number of chips (if bags are chosen at random the prior probability is equal). Their posterior probabilities (i.e., their guesses) are related and determined by the prior probability; and the process of drawing poker chips to guess at the probability of particular poker chips follows a Bernoulli process. In the real world, however, the prior is often unclear (and difficult to control) and varies from setting to setting and individual to individual. For example, an individual at a pawn shop in a particular neighborhood may have different priors about the quality of an electronic item than that same individual at Best Buy, and an individual familiar with the neighborhood may have different priors than an individual unfamiliar with the neighborhood. Additionally, in the real world, the decision making model is not a simple one (e.g., Bernoulli process). And there is no normative or “public model” of what may be the most efficient and informative way to make a decision, and therefore it is very difficult to identify what may be a sub-efficient (pathologic) or super-efficient (successful) way to make a decision.

Considering performance-based measures of physical function conducted in the lab, individuals are given explicit instructions prior to completing the task. For example in the fast-paced gait

speed test, individuals are told to “walk at a rapid pace as fast as you can, and go all the way to the other end of the course.” They are explicitly instructed to walk at their maximal capacity for a designated duration. Individuals then perform that instructed task with the explicit goal of completing the task to their maximal capacity. All individuals tested are given the same prior instructions, the environment of the test is typically identical, and - assuming that all individuals are attempting the test at their maximal capacity – when considering all the individuals in a given study, their outcomes are a reflection of the true differences in maximal capacity conditional on the prior instructions and testing environment. The real world can vary substantially from the laboratory. One way to examine how those environments vary is by considering each type of performance-based test (Figure 5).

A battery of performance-based tests, ranging from the 4-meter walk (test at usual speed) to lifting a book to above the shoulder level (test of ability to perform the task or not) are often administered to individuals in the laboratory. In the real world, however, tasks arranged together that span function (e.g., a “battery”) may or may not occur. Whether or not an individual lifts a book to above shoulder level in a given week provides no indication of whether the individual is actually able to lift a book to above shoulder level or not. Some individuals may be unable to do the task and that is why the task does not occur, and other individuals are able to do the task, but have no reason to complete the task and that is why the task does not occur. Tests of maximum capacity are also often administered to individuals in a laboratory. Performing at maximal capacity may or may not occur in the real world. If we consider activity across 24 hours, it may actually be inefficient to expend maximal energy on any one activity and underperform on other activities as a result. Additionally, in a lab context walking at maximal exertion may be tested where the motivation is to perform the task according to the directions. In the real world, some motivations (e.g., catching the last bus of the day back home) may more accurately measure maximum capacity than a laboratory test.

The real world is also a much more complex environment than the laboratory. In the clinic, evaluators can test grip strength by asking an individual to sit comfortably on a chair, extend his/her right hand to grasp a dynamometer, and squeeze the handles as hard as possible. All factors other than grip strength are controlled in order to isolate a measure of upper extremity strength. In the real world, gripping an object (e.g., a can opener) may occur while walking or

standing, and while considering the directions to a recipe. The task requiring upper extremity strength occurs while an individual is also stabilizing or moving (lower extremity strength) and thinking (cognitive activity). Some performance-based laboratory tests measure two tasks simultaneously. For example, the dual tasking gait assessment has participants perform cognitive tasks (e.g., serial 7 subtractions out loud) while walking at their “usual” pace¹¹³. Laboratory tests of gait augmented with virtual reality also are used to better reflect the multiple domains required to walk in everyday environments.¹¹⁴ The key difference between common laboratory assessments of physical function, like gait, and the real world is that accomplishing tasks in the real world, like walking, place cognitive demands on individuals that often do not exist in the lab. Executive function, for example, plays an important role in the regulation of gait particularly when individuals need to make decisions in real time, including avoiding obstacles and performing other tasks¹¹⁵.

Unlike in the lab, the socio-cultural factors and the built environment that characterize the real world can also have a significant impact on activity. For example, individuals living in low socioeconomic areas – independent of physical function differences – may be less active due to fewer activity related facilities and restrictive environmental and neighborhood characteristics^{29, 116-120}. Clutter, poor lighting, and other environmental factors can significantly impact gait and can lead to falls and disability¹²¹. The availability of both human and non-human help or compensatory strategies (e.g., a relative assisting with walking and the use of a cane or other assistive device) can also significantly affect the types of activities completed as well as how they are completed. Within the lab, two individuals may score similarly on performance-based tests of physical function. However, in the real world due to various factors, performance-based tests of physical activity may vary considerably.

Levitt and List, two economists, discussed three considerations that can impact whether lab findings can be extrapolated to the real world: “1) The nature and extent to which one’s actions are scrutinized by others; 2) The particular context and process by which a decision is embedded; 3) self-selection of the individuals making the decisions.”¹²² While these considerations were developed based on economic test theory, they are applicable to our discussion. While economists may be interested in “scrutiny” or changes in decision making that may occur when someone is watching, for our purposes, scrutiny can simply relate to how within an integrated

community (e.g., family), individuals do not act independently. Individuals in the real world are operating in highly complex, hierarchical, and dependent environments where one's actions are connected to others through feedback loops. Additionally, individuals are embedded in different contexts and have different paradigms that can impact decisions and activities. For example, there may be cultural variation to the endorsement of familial support ¹²³, which can impact levels of activity. Finally, performance in the laboratory and performance in the real world may be effected by subject level characteristics including education, occupation, need for approval, and perceptions of authority. ¹²²

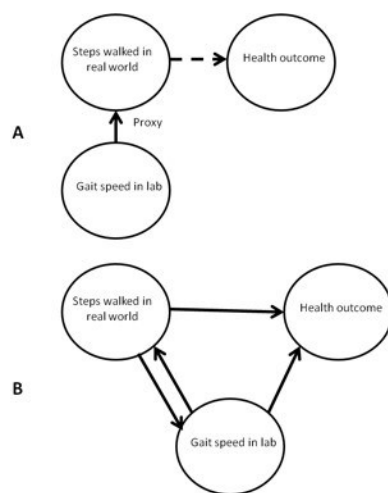


Figure 6. Model [A] and [B] explaining the relationship among steps walked in the real world, gait speed measured in the lab, and health outcomes

As indicated above, discordance between performance-based tests of physical function in the laboratory and performance-based tests of physical activity in the real world may be expected. The direction of discordance, or whether individuals over- or underachieve in the real world compared to the lab, is unclear. Glass also came to this conclusion, stating that “many older persons appear to be both overachieving and underachieving in their functional performance...this discordance appears to be relatively symmetrical...” ³⁹ While Glass was mostly concerned with discordance between hypothetical and enacted functioning based on self-report of the same functional question with

only the tenses changed, our discussion of discordance is between two different performance-based tests: physical function and physical activity. In order to understand whether discordance is a deviation from the norm, we should first consider whether we should expect concordance between these tests.

As an example, consider gait speed, a performance-based test of mobility, and steps walked measured with a pedometer, a performance-based test of physical activity. Gait speed can be performed at usual as well as maximum capacity, and is a measure of functional mobility and is often used as a proxy for community walking ^{124, 125}. Steps walked is an objective measure of community walking, or walking in the real world, and is also a measure of functional mobility. There is a large body of evidence suggesting that gait speed can predict important health

outcomes including mortality ¹²⁶, disability ¹²⁷, and health care utilization ⁶². Figure 6 describes two main ways to understand this association. In [A], gait speed in the lab is a proxy measure for steps walked in the real world, and the associations with health outcomes are due to the associations between steps walked in the real world and health outcomes. In [B], gait speed in the lab and steps walked in the real world are related but different measures that are both associated with health outcomes. If we believe model A, then we should expect concordance with steps walked in the real world, and any discordance independent of measurement error, can be explained by the complexity of walking in the real world. If we add other measures, including balance and cognition, we will create an increasingly more accurate and precise proxy measure of steps walked in the real world (Figure 7). If we believe model B, then we should expect some concordance with gait speed and steps walked, and discordance can be explained as variance in

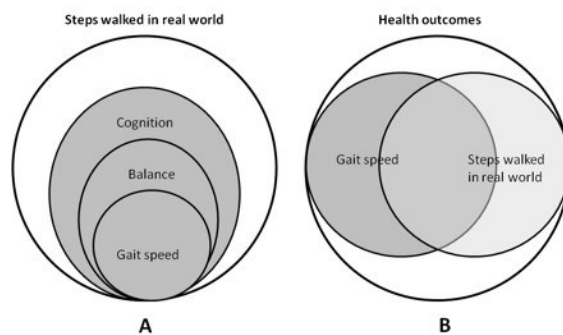


Figure 7. Concordance and discordance in measures by model

functional mobility or health outcomes that are independently attributable to both gait speed and steps walked. For example, steps walked in the real world is a measure of mobility that is dependent on variables not measured by gait speed including balance, cognition, and socio-cultural and environmental characteristics.

These factors in total are related to health outcomes. Gait speed measured in the lab also includes metrics that cannot be measured or may not be performed in the real world (e.g., maximum capacity) that are also related to health outcomes.

The model we believe or choose has important consequences. Let us consider the relationship between gait speed and dementia. A number of recent studies have indicated that slowed gait speed predicts dementia ^{3, 11, 128}. Studies have also indicated that physical activity, both self-report and total daily activity measured using an accelerometer, is cognitively beneficial ^{22, 24, 129} and associated with reduced incidence of dementia ^{23, 130, 131}. One explanation of the relationship between gait and dementia is that gait depends on and requires cognitive function, as indicated by the results of numerous studies using dual task gait assessments ¹⁴. These studies indicate that

+++++ Slowed gait speed may be more predictive of non-Alzheimer's type dementia (e.g. Vascular dementia)

walking is a cognitively complex task that requires executive function and attention (e.g. ¹³²). Other studies indicate that changes in gait speed may be the result of cerebrovascular lesions and therefore slowed gait is an early indicator of a long disease course that leads to dementia ¹¹. The relationship between physical activity and dementia has been explained by multiple mechanisms ¹³³ including increased cerebral blood flow ¹³⁴, up-regulation of neurotrophic factors resulting in CNS benefits including neurogenesis ^{18, 21}, and environmental enrichment models suggesting that physical activity in the context of social and cognitive activity may be beneficial ^{135, 136}. These diverse mechanisms suggest that physical function measured in the lab by gait speed and physical activity measured by steps walked in the real world may be performance-based measures that reflect different components of walking or mobility that are associated – through multiple mechanisms – with dementia. This in turn suggests that model B may be a more informative and accurate model of the relationship between gait speed, steps walked, and health outcomes.

Physical movement as a biometric signal

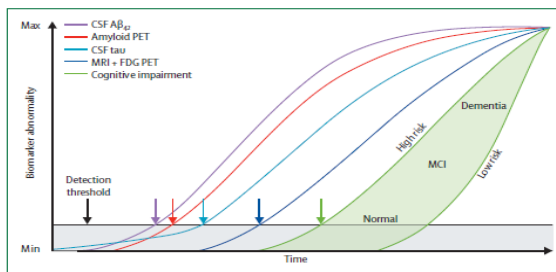


Figure 8. Model integrating Alzheimer's disease immunohistology and biomarkers.

Model B further suggests that we can develop a framework where we integrate performance-based measures of physical function and physical activity to better understand the sequence of mobility change from birth to disease (e.g., disability). If we can extract signals from each measure that are

clearly defined, we can build a similar model to that developed by Tim Salthouse (¹⁰⁷) and Clifford Jack (Figure 8; ¹¹¹). While Salthouses's findings rely heavily on cross-sectional data (see ¹⁰⁹ for criticism of Salthouse's assertions), his research on life course trends in cognition are essential to a fundamental understanding of what may be normal aging, and how deviations from that can be considered pathological (or successful ¹¹⁰). In Jack et al.'s work on pathological cognitive aging related to Alzheimer's disease (AD), Clifford Jack and colleagues developed a model integrating AD immunohistology and biomarkers across time from birth to diagnosis of mild cognitive impairment (MCI) and dementia ¹¹¹. His work provided a compelling argument for the importance of various measures of cognitive decline and impairment considering the sequential trajectories of each over the life course as well as the detection threshold. This model of the cascade or

sequence of events does the following: 1) provides insight into the etiology of the disease; 2) clearly indicates how various measures of cognitive decline, ranging from blood biomarker to behavioral measures, may be more or less relevant depending on the stage of the disease; and 3) helps identify windows of intervention where researchers may be able to intervene to delay or reverse decline and measure intervention response.

The models developed by Salthouse and Jack are relevant to physical function, physical activity, and disablement because currently there is not a clear model (or an empirically tested model) of how physical function and physical activity may change over the life course, how different subdomains of physical function and physical activity (see Figure 8) may change or decline and in what sequence, and how various measures of physical function and physical activity may be more or less relevant depending on age (in the case of normal decline) or the stage of pathology in the case of age-related disease ****. If we consider physical function and activity measures as biometrics or biomarkers, we can add specific metrics of performance-based measures in sequence that are most sensitive to various stages or dimensions of decline (or incline for certain stages prior to the onset of pathology). This model will be outcome specific. For example, we may expect a different sequence or cascade of mobility change for cognitive disability or dementia than we may for physical disability.

As an example using the outcome cognitive disability, consider the trajectory of mobility change related to the development of AD. Prior to the onset of cognitive impairments we expect subtle

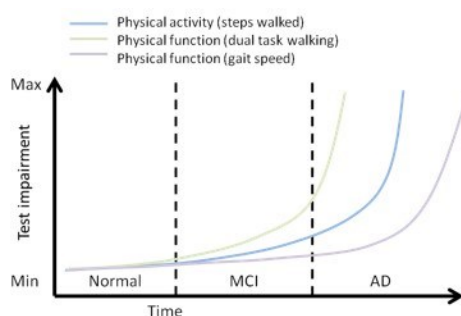


Figure 9. Hypothetical model of change in physical function and physical activity as individuals progress from normal to MCI to Alzheimer's disease (AD)

physical function and physical activity changes that are related to decreases in muscle strength and balance associated with aging. These are changes that can be considered age-related and not pathological or associated with a particular impairment trajectory. Additionally, we may expect physical activity changes related to changes in occupation and environmental changes (e.g., changes in neighborhood walkability).

**** While unrelated to the focus of this discussion of age-related change, changes in physical function related to Parkinson's and other movement related pathologies have been clearly delineated.

Again, these are not changes that we consider related to pathology. As individuals who will eventually be diagnosed as AD begin their 6th decade, they may begin to experience sub-clinical and sub-conscious levels of cognitive impairment associated with AD. These changes may be reflected in subtle gait and balance changes; measures of dual task walking, for example, may be sensitive to these changes (vs. parameters/ metrics from usual walking). As individuals progress from normal cognition to MCI, depending on the subtype (amnesic or non-amnesic), we may expect different gait changes associated with declines in memory or declines in other cognitive domains (e.g., executive function). As individuals are diagnosed with AD and progress from early to late stages, we can also expect gross gait changes that can be measured by usual walking tests and observation. For physical activity, we should also expect activity changes as individuals progress from normal to MCI to AD. Individuals may first begin to alter their activity patterns due to an inability to complete leisure time activities. These patterns may further be altered as they are unable to complete ADLs and IADLs. Figure 9 describes a hypothetical model of these changes based on the model developed by Jack et al.

Future: the “quantified self”: lab measures in the real world

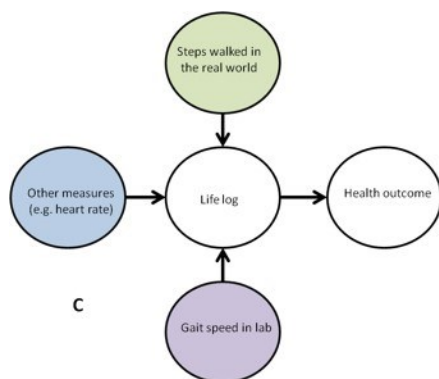


Figure 10. Model C: The life log may incorporate a range of important health measures to predict health outcomes

Model A described above (Figure 7) considers steps walked in the real world as the gold standard for mobility – or the perfect measure that incorporates all aspects of physical function and physical activity related to mobility. While this is clearly not the case for pedometer measured metrics of mobility, we are rapidly moving towards a future where we may be able to unobtrusively measure and collect everything – a life log. The quantified self is a movement to incorporate technology to acquire data on all parts of a person’s life, ranging from biologic signals to physical

movement and amount of food consumed¹³⁷. The recent surge in commercial activity monitors, including the Fitbit and Jawbone, as well as sleep monitors, diet and weight monitors, and heart monitors indicates that technology has sufficiently progressed to allow for unobtrusive monitoring of many bodily functions and activities using body-worn devices. The future life log

may be able to incorporate lab-measured gait parameters, steps walked, and other measures to predict health outcomes (Model C; Figure 10).

Already, researchers are beginning to use accelerometers to measure multiple parameters that traditionally were in the domain of either lab-based tests or real-world tests. These body-worn devices can collect physical activity measures beyond steps walked, including frequency, duration, and intensity of activity, as well as physical function measures, including gait variability and other stride dynamics. Accelerometers can measure acceleration across multiple axes at defined intervals (from milliseconds to minutes). This allows researchers to potentially measure sensitive physical activity metrics including bouts over a specified interval, maximum intensity of activity within a defined interval, and number of active and inactive periods of time⁹¹. Additionally, these devices may provide similar and validated metrics to those derived using force sensitive insoles in lab-based gait tests^{138, 139}. This suggests that we can reasonably expect to collect multiple metrics across physical function and activity domains within a population without having individuals attend expensive, resource intensive, lab-based evaluations.

The implications for this novel type of data collection are vast. There are a number of companies currently collecting data passively in order to inform health care providers about health and behavioral data in between clinical visits (e.g., ginger.io¹⁴⁰). These companies utilize the computing power, pervasive use, and natural integration of Smartphones into many individuals' daily lives to collect behavioral data ranging from physical activity (via built-in accelerometers) to mood (via self-report questionnaires administered via the phone) in order to identify at-risk patients and alert health care providers or caregivers. While we now have the ability to collect massive amounts of data, partially due to the impressive computers many of us keep in our pockets, understanding the data signals and signatures that indicate pathology, decline, or an acute event requires expertise across multiple disciplines including computer science, medicine, rehabilitation, physical therapy, epidemiology, biostatistics, and engineering.

Specifically, for physical activity and physical function, decades of research has helped us understand the mechanical properties of walking, alterations in gait that are related to pathology, duration, and intensity of physical activity that may be beneficial, and interventions that may be successful at increasing or benefiting physical activity and physical function. The next stage of this

work is translating this knowledge to an understanding of signals obtained from passive, body-worn devices or sensors that are the next generation of data collection.

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Chapter 8.

Summary and conclusions

Specific Aims

Aim 1a: Explore adherence to physical activity guidelines and the cross-sectional association between objective and self-report measures of low-intensity physical and walking activity and physical function.

In our community-based cohort of urban-dwelling older adults within the Baltimore Experience Corps Trial (BECT), we found a wide discrepancy between objective and self-report measures of adherence to physical activity guidelines. Similar to findings in previous studies (e.g., ¹), the vast majority (approximately 93% using the 10,000 steps/day guideline and 99% using the 30 minutes of moderate-intensity walking activity/day guideline) of participants did not meet guidelines using objective measures while the majority of participants (approximately 62%) did meet guidelines based on self-report moderate- to vigorous-intensity physical activity/ week. This discrepancy is partially explained by expected over-estimation of physical activity using self-report measures, as well as differences between walking activity and physical activity where walking activity is not synonymous with and represents only a significant component of total physical activity. Generally, within the BECT, the majority of physical and walking activity was in the low-intensity range.

Low-intensity walking activity measured by the objective step activity monitor (SAM) was associated with the majority of physical function measures, and these associations remained significant for walking, leg strength, and lower extremity strength when including moderate-intensity walking activity as a covariate. Conversely, low-intensity physical activity measured by the Community Health Activities Model Program for Seniors (CHAMPS) questionnaire was not associated with any physical function measures, while moderate- to vigorous-intensity physical activity was associated with all measures independent of low-intensity physical activity. These results suggest that low-intensity walking activity may be associated with physical function; however this range of activity may be difficult to measure using self-report measures. Additionally, findings support physical activity guideline recommendations to increase moderate-intensity physical activity in order to preserve physical function, and encourage additional exploration into the benefits of low-intensity walking and physical activity specifically using objective measures.

Aim 1b: Explore the cross-sectional association between objective and self-report measures of low-intensity physical and walking activity and cognitive function/ brain health.

In our community-based cohort of urban-dwelling older adults within the BECT who were at elevated risk for cognitive decline due to age, low income, low education, and a high number of chronic disease, low-intensity walking activity measured by the objective SAM was associated with both behavioral and brain structural measures of memory in women. The association with the hippocampus was independent of moderate- to vigorous-intensity walking activity and seemed structure specific considering the lack of a significant association with the thalamus, used as a control region. These findings underscore the importance of exploring whether modest and achievable increases in non-exercise, lifestyle physical activities in the low-intensity range may promote cognitive health related to memory and reduced risk of dementia. The results additionally expand prior evidence indicating that increasing exercise and cardiovascular fitness may be associated with benefits to memory considering both cognitive function and brain health measures ²⁻⁴, and encourage future research to explore whether the cognitive benefits of non-exercise, lifestyle activities physical activities may occur through molecular pathways unique to those of exercise.

Similar to findings reported under Specific Aim 1a above, self-report CHAMPS measures of physical activity were not associated with cognitive function or brain structure. Again the lack of an association may be driven by measurement insensitivity and other measurement issues inherent to self-report questionnaires particularly when exploring physical activity within the low-intensity range.

Aim 2a: Explore whether the EC intervention was associated with increased walking activity measured by an objective physical activity measurement device.

Within the Brian Health Study, a physical activity and neuroimaging sub-study within the BECT, we found that women randomized to the EC intervention showed significant increases in total and low-intensity walking activity at 24 months compared to their sex-matched control group. We did not observe increases in moderate- to vigorous-intensity walking activity in women. Men

randomized to the intervention group showed decreased moderate- to vigorous-intensity walking activity at 12 and 24 months compared to their sex-matched control group. These results suggest that a community-based intervention that naturally integrates activity within urban areas may effectively increase mostly low-intensity walking activity in women, who – compared to men within the BECT - had lower levels of baseline walking and physical activity, and greater chronic disease burden.

The BHS was specifically designed to measure physical activity (specifically walking activity) outside the actual intervention. The goal of this study design was to measure whether the Experience Corps intervention may reset trajectories of physical activity while participants are outside the intervention. The intervention specific increase in walking activity in women suggests that volunteering in the schools, which requires engagement in social, cognitive and physical activities ⁵, may have led to the maintenance of physical activity, compared to expected age-related declines observed in the control group. For individuals at high levels of physical activity, EC may not be an appropriate intervention to increase physical activity. Because EC was not designed as an exercise intervention, perhaps it may be expected that it may not increase activities associated with moderate- to vigorous-intensity walking activity. For men within the intervention group, EC may have served to increase social and cognitive activity, which may have reduced levels of moderate-intensity walking activity. Small sample size and attrition may also have contributed to the lack of an effect on total and low-intensity walking activity. Generally, these findings provide compelling evidence for a community-based model of health promotion that, through increasing walking activity, may address disparities in health in an at-risk population of older adults.

Aim 2b: Explore whether the EC intervention was associated with increased physical activity measured by a self-report physical activity questionnaire.

Within the BECT, we found that women in the control and intervention group showed significant declines in physical activity at 12 and 24 months; we additionally observed a negative intervention effect at 12 and 24 months for total and moderate- to vigorous-intensity physical activity respectively. We observed significant declines in total physical activity at 24 months and moderate- to vigorous physical activity in men in the control group at 12 and 24 months, and a

significant positive intervention effect for low-intensity physical activities for men at 24 months. These findings generally indicate that the EC intervention did not have an effect on age-related declines in physical activity in women, and may have reduced total physical activity within the short term (12 months) and reduced moderate- to vigorous physical activity by the end of the trial (24 months). These conclusions must be considered in terms of the lack of sensitivity of self-report measures of low-intensity physical activity as well as the modification of the CHAMPS used in the BECT to focus on moderate- to vigorous-intensity physical activities. Additionally, as mentioned above under Specific Aim 2a, EC is not an exercise intervention and therefore may not be expected to increase activities associated with moderate- to vigorous-intensity caloric expenditure.

For men, maintenance physical activity by the intervention group – relative to significant declines in the control group – and the positive intervention effect for low-intensity physical activities observed at the end of the trial (24 months), suggest that within this larger male sample (relative to the smaller BHS sample used in Specific Aim 2a), the EC intervention may have positive intervention related benefits and may be an effective intervention for men. In addition to greater power to observe intervention effects in males, one potential explanation for this reverse effect (considering Specific Aim 2a) is that a community intervention like Experience Corps may not affect individuals similarly. As explained in a prior study ⁶, sex-differences in roles within the schools may be expected considering the context of an elementary school system with majority female teachers as well as a community with majority female heads of household. These differences may have driven positive intervention effects in men.

Aim 3: Explore the relationship between physical activity and physical function in order to inform the use of objective physical activity devices as biometric signals to predict cognitive decline and disability.

Recent evidence from older adult patient and community-dwelling populations suggests that abnormalities in physical function, including mobility, and physical activity are associated and predictive of future cognitive decline, MCI, and dementia ⁷⁻¹¹. In order to understand the mechanistic or biologic relationship between physical movement as a broad category including both physical function and activity, and cognition, it is extremely important to understand the

relationship between physical function and activity, and understand how we may be able to sensitively measure these variables in larger populations in order to develop measures and metrics to best predict future declines and design and test interventions.

Physical function and physical activity can be conceptualized as the relationship between “could do” within a lab setting and “do do” within a community setting. Measurement of both these domains should be considered in terms of how the specific metric corresponds to different dimensions of the disablement model ^{12, 13}. Specific to performance-based measures of physical function, we can understand measures in terms of how predictive they may be of different stages of disablement, and then try to understand how performance based measures of physical activity may be similar or different (and how) from physical function measures.

The development of accelerometer technologies which allow researchers to measure objective, performance-based measures of physical function and activity, allow for the collection of vast amounts of data fairly unobtrusively within a community setting. Understanding the biometric signals of these data and developing accurate and distinct measures of physical function and activity provide the opportunity to better characterize trajectories across the life course and characterize how those trajectories may change due to cognitive decline and how those signals may offer early signs of future decline.

General summary and conclusions

In summary, objective measures of physical activity within the low-intensity range were associated in cross-section with physical function and both behavioral and structural measures of brain structure. These objective measures, which are important in order to characterize physical activity and change particularly within the low-intensity range, captured increases in total and low-intensity walking activity associated with the intervention in women within the BECT, and a decrease in moderate- to vigorous-intensity walking activity in men. Self-report measures of physical activity did not sensitively capture low-intensity physical activity or the relationship between physical activity and cognition; however, as expected, sensitively captured moderate- to vigorous physical activity and its association with physical function. Self-report measures additionally indicated declines across both intervention arms in women within the BECT and

marginal negative intervention effects particularly in moderate- to vigorous-intensity physical activity, and captured declines in the control group for men, and positive intervention effects at 24 months. Objective measures are extremely useful in order to sensitively capture physical activity, and can be used in order to better measure and understand the relationship between physical function/ activity and cognition.

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Curriculum Vitae

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EDUCATION

Post-doc, National Institute of Aging (2015)

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PhD, Johns Hopkins Bloomberg School of Public Health, Department of Mental Health (2015)

Thesis: The association between physical activity and cognition

MPH, Johns Hopkins Bloomberg School of Public Health (2011)

GPA: 3.80

BA, Duke University (2005)

Major: English, GPA: 3.70; African American Studies, GPA: 3.90

POSITIONS

- Senior Research Program Coord. and Data Manager, Center on Aging and Health, Johns Hopkins, 2007 – 2015
See Lab Website: www.carlsonlab.org
- Research Program Director, Center for Africana Studies, Johns Hopkins, 2014 – present
See Affiliated Faculty profile: <http://krieger.jhu.edu/africana/directory/vijay-r-varma/>
- Project Manager, Kites Corporation, International Department, Tokyo, Japan, 2006 – 2007

AWARDS & HONORS

- Morton Kramer Award, excellence in biostatistical and epidemiologic methods, Department of Mental Health, Johns Hopkins (one awarded to a graduating doctoral student), 2015
- Ruth L. Kirschstein National Research Service Award (NRSA) Epidemiology and Biostatistics of Aging Fellow, 2014 – 2015
- National Institute on Aging (NIA) Junior Investigator Travel Award, 2014
- Ruth L. Kirschstein National Research Service Award (NRSA) Aging and Dementia Fellow, 2011 – 2014
- National Science Foundation (NSF) Wireless Health Travel Award, 2013
- Johns Hopkins Institute of Applied Economics, Global Health and the Study of Business Enterprise (IAEGHBE) Graduate Student Travel Grant, 2012
- Johns Hopkins Urban Health Inst. Student-Community grant recipient (one of six awarded to grad. students), 2010
- Roothbert Fellow (Roothbert Fund, Inc.), 2009 (<http://www.roothbertfund.org/>)
- Warren E. Miller & Gail H. Bates Maryland House of Delegates Scholar, 2009
- USA funds Access to Education Scholar, 2009
- Duke University Women's Studies Gender and Race Award (one of two awarded to undergraduate and graduate students), 2005
- Duke University English Department graduation commencement speaker, 2005
- Duke University Undergraduate Research Symposium Grant, film documentary work in Trinidad, 2005
- Duke University Undergraduate Research Symposium Grant, study at Oxford University, 2004

- Duke University African American Studies Travel Grant, study at the Indian Institute, Oxford University, 2004
- Duke University Service Opportunities in Leadership Fellowship (one of eight awarded), Terry Sanford Institute of Public Policy, 2004
- Duke University Women's Studies Travel Grant, Tanzania, 2003
- Duke University Dean's List, 2003-2004
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PUBLICATIONS (peer reviewed)

1. Hughes TB, **Varma VR**, Pettigrew C, Albert MA. African Americans and clinical research: evidence concerning barriers and facilitators to participation and recruitment recommendations. *Gerontologist*. 2015. Accepted.
2. **Varma VR**, Tan EJ, Gross AL, Harris GC, Rebok GW, Romani W, Fried LP, Carlson MC. Effect of community volunteering on physical activity: a randomized clinical trial. *American Journal of Preventive Medicine*. 2015. In Press.
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PUBLICATIONS (book chapters & other non peer-reviewed)

1. Carlson MC & **Varma VR**. Non-pharmacological interventions and dementias. *Oxford Textbook of Geriatric Medicine, 3rd Edition*. (Eds Michel J, Beattie L, Martin FC, Walston J) Oxford University Press. Accepted
2. Carlson MC & **Varma VR**. Activity and Neurocognitive Health in Older Adults. *Neuropsychology of Cardiovascular Disease, 2nd Edition*. (Eds. Waldstein SR & Elias MF) Taylor & Francis. 2013
3. Kasper JD, Edwards B, Freedman V, Bruce T, Weiss C, Seplaki CL, Guralnik J, Plassman BL, Wallace R, Carlson MC, **Varma VR**, Niefeld M. Advances in Survey Assessment of Disability in Older Adults: Measuring Physical and Cognitive Capacity in the National Health and Aging Trends Study (NHATS). *Proceedings from the 10th Conference on Health Survey Research Methods*. 2011

PUBLICATIONS (currently under review/ in process)

1. Tang X, **Varma VR**, Miller MI, Carlson MC. Sex-dependent correlations between education and the volume and shape of the hippocampus and the amygdala in older adults. *Under review*.
2. Carlson MC, **Varma VR**, Adam A, Zipunnikov V, Crainiceanu CM. Using GPS and accelerometer technologies to measure activities related to cognitive and brain health. *Under review*
3. **Varma VR**, Zipunnikov V, Adam A, Crainiceanu CM, Carlson MC. Concepts and metrics: merging GPS and accelerometer technologies to better understand and measure physical activity. *In process*
4. Carlson MC, Gross AL, Betz J, Xue QL, Chuang YF, **Varma VR**, Parisi JM, Seeman TE, Tanner EK, Tan EJ, Gruenwald TL, McGill S, Albert MA, Fried LP, Rebok GW. Cognitive benefits of a social engagement program: the Baltimore Experience Corps randomized, controlled trial. *In process*

SELECTED INVITED CONFERENCE PRESENTATIONS

Varma VR, Harris GC, Tan EJ, Gross A, Rebok GW, Carlson MC. Increases in physical activity as a result of Experience Corps participation. NIA junior investigator travel award recipient poster presentation at CNS conference at the *Gerontological Society of America* annual meeting, Nov 2014 (Washington DC).

Varma VR, Chuang YF, Harris GC, Carlson MC. Daily walking activity is associated with hippocampal volume in older adults. Poster presentation at the *Cognitive Aging Conference* 2014 (Atlanta, GA).

Varma VR, Harris GC, Tan EJ, Gross A, Rebok GW, Carlson MC. The effect of Experience Corps on life-style physical activity. Symposium talk at the *Gerontological Society of America* annual meeting, 2013 (New Orleans, LA)

Varma VR, Adam A, Harris GC, Carlson MC. Mobile technology to measure activities related to cognitive health in older adults. Travel grant recipient poster presentation at the *Wireless Health*, 2013 (Baltimore, MD).

SERVICE

- Ad-hoc Reviewer: *Neurobiology of Aging; Journal of Gerontology: Medical Sciences; Prevention Science; Health Promotion International; Journal of Applied Gerontology*

- Advisory Committee: Center for Africana Studies (2014 –)
- Trustee, Board of Directors: Boy Scout Troop 368 Alumni Association (2012 –)
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- Admissions Committee member: Roothbert Fund, Inc. (2010 – present)
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REFERENCES

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PERSONAL

- Contributing writer, *www.chopsticksny.com* (Japanese culture magazine, New York, NY): 2007 – 2009
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